HYPERTENSION
AND
NEPHRITIS

By

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TO

THE MEMORY OF MY FATHER

DR. MAURICE FISHBERG

PREFACE TO THE FIFTH EDITION

Over fifteen years have elapsed since the last revision. During this period, few aspects of renal and hypertensive disease have failed to share in the progress of medicine. As is usually the case, advance has been not only by acquisition of new knowledge but also by fall from grace of much previously accepted; the inevitability of a considerable degree of scientific obsolescence is painfully brought home when a book is revised after a decade and a half. While World War II diverted scientific investigators from some of the fields included in this book, the tragedy accelerated progress in others. Enormous experience with traumatic shock established beyond peradventure the great rôle of prerenally engendered diminution in perfusion of the kidney in the pathogenesis of acute renal insufficiency. Much has been learned since the War about disturbances in electrolyte economy resulting from functional impairment of the kidney, and bedside application of this newer knowledge has been greatly facilitated by the advent of the flame photometer With the advantage of hindsight, it is puzzling why as common and distinctive a renal lesion as that of diabetic glomerulosclerosis was not differentiated until so recently. Likewise, only within the past few years has the great frequency of chronic pyelonephritis been generally recognized. Most basic of all recent progress in study of renal disease, however, has been clinical application of measurements of renal blood flow, glomerular filtration and some of the tubular functions in Bright's disease. They have imparted to investigation of the pathological physiology of renal disease the beginnings of that quantitative formulation which is the goal in all branches of science. These advances have brought in their wake better founded and more [illegible]
renal fun[illegible]

Genera[illegible]

[illegible] years have [illegible] assessment of sympathectomy with the perspective of long-term observation, re-popularization of maximal sodium restriction and, most recently, application of hypotensive drugs much more efficient than those previously available While none of these therapeutic modalities is basic

or more than symptomatic, their use has added to the comfort, the ability to work and the life-span of many hypertensives. Perhaps equally important has been the general appreciation of the innate benignity of many hypertensive states with consequent avoidance of superimposition on high blood pressure of iatrogenic symptomatology and invalidism.

In the effort to depict these and many other advances, the book has been rewritten. Seven new chapters have been added on the individual processes in urine formation, diabetic glomerulosclerosis, chronic pyelonephritis, dietetic, pharmacologic and surgical treatment in essential hypertension, and hypertension in pheochromocytoma and Cushing's syndrome. Every effort has been made to minimize enlargement of the book, but it has not been entirely avoidable. The book is written from consultation room and bedside by a practitioner for practitioners, but I hope it will also be of value to medical students and house officers. Sight has not been lost of the fact that the vast majority of individuals who suffer from hypertensive and renal diseases, which are so common and often last for decades, are, fortunately, taken care of by the family physician, whose laboratory facilities are often limited.

My wife, Irene L. Fishberg, has helped at all stages of the writing of the manuscript and the correction of the proof. *Dr. Ella H. Fishberg, Biochemist to* Beth Israel Hospital, has been a powerful support in matters chemical.

A. M. F.

New York, N Y.

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Chapter I

CLINICAL CORONARY HEART DISEASE AND CORONARY ARTERY ATHEROSCLEROSIS

Coronary heart disease is a clinical entity; coronary atherosclerosis (or arteriosclerosis), a pathological entity. A considerable body of scientific evidence links these two entities Yet much confused thinking is generated because of the failure to separate them and to realize their truly separate natures: Indeed, major elements of the progress made in the understanding of clinical coronary heart disease and its prevention have been possible only by a separation of the considerations of these two entities

CORONARY ARTERY ATHEROSCLEROSIS

The coronary arteries, along with medium-sized arteries elsewhere in the body, are the seat of a disease process characterized by a thickening of the intimal coat of the arterial wall The normal, undiseased coronary artery has practically no tissue in the intimal layer between the endothelial lining and the internal elastic membrane The pathologic essence of the major disease process which affects the coronary arteries is an accumulation of inert material and tissue within this intimal coat, internal to the internal elastic membrane Diverse chemical and structural elements are found to make up the material which accumulates within the intima of diseased coronary arteries Among these materials are lipids of various sorts, calcium salts and even calcium in the form of bone, fibrous and fibro-elastic tissue, hemorrhagic areas, and areas of thrombosis at various stages of organization

There exist several views concerning the pathogenetic sequence of events in the development of the mature arterial lesion. Largely such views differ with respect to the early stages of the development of the lesion and with respect to the structural feature considered as primary. One concept attributable to Rokitansky[1], and more recently to Duguid[2], is that thrombosis is the primary event in the artery and that the remaining morphologic features of the lesion are in some way a later result of such thrombosis. A second view, originating with Winternitz, Thomas, and Le Compte[3], holds that hemorrhage into the intimal part of the artery wall from vasa vasora is the primary process, all other features representing various aspects of the tissue reaction to such hemorrhage. A third view is centered around the lipid elements of the arteriosclerotic lesion. Anitschkow[4] proposed that lipids from the circulating blood infiltrate through the endothelial lining and there set up the original lipid deposits which initiate reactive changes on the part of the body with ultimate development of the full-blown lesion. More recently, there is the view of Rinehart and Moon[5] that alterations in the mucopolysaccharide structure of the ground substance of the arterial wall is the initiating feature of the lesion and that the other aspects of the lesion are secondary to this. In support of each of these various views there are structural features and elements of biological evidence which suggest possible validity. Unfortunately, however, the proponents of each of the views concerning the primary materials which constitute the arteriosclerotic deposit have felt at times the necessity of insisting upon that primacy to the absolute exclusion of all other possibilities What is worse they have misinterpreted their privileges in this regard in that by insistence on a particular view of the primary structural element they have stated directly or indirectly that an entire body of biochemical, clinical, and other evidence (which body of evidence is entirely self-sufficient) must be incorrect. One is certainly entitled to entertain any view of the primary facets involved in development of the arteriosclerotic lesion It is encouraging that various investigators have given much thought to possible modes of pathogenesis of this disease, but when such views are used to run head-on into solidly-established clinical and biochemical evidence, we reach an impass which is patently ridicu-

lous. A view which is clearly in opposition with *facts* simply needs modification because it cannot be correct. It may not be completely incorrect but it certainly needs modification.

Perhaps a more fruitful approach to the entire problem is to recognize the existence of various structural features of the coronary arteriosclerotic lesion and to look forward to the time when an integrated concept of the origin and pathogenesis of this disease will allow for the proper placement of each such structural feature. Insistence upon primacy of a particular feature at a time when such primacy cannot be established can serve only to impede progress which would otherwise be possible. It is largely from considerations such as these that the author of this book prefers the term used by Goldblatt[6] to describe this lesion, namely, "simple intimal arteriosclerosis" rather than "atherosclerosis." In this way one eliminates the prejudicial view that the lipid element of the lesion is either primary or most important as is suggested by the origin of the term "athero." Many of the arterial lesions show very little lipid at that particular point in time when the pathologist has the opportunity to examine the tissue. Unfortunately, when such lesions are termed "atherosclerotic lesions," certain investigators take great offense because they can argue that there is no "athero" element to be found. Such controversy can be eliminated by the use of the term "simple intimal arteriosclerosis" to encompass at this time those lesions which result in the accumulation of tissue or inert material between the internal elastic membrane and the lumen of the artery and which have the ultimate effect of narrowing the lumen of that artery.

It is now fairly widely agreed as a result of careful pathological studies, including the injection studies of gross specimens, such as the classical ones of Blumgart and Schlesinger[7], the microscopic pathological studies of Spain and co-workers[8], and of Dry, Edwards and White[9] that coronary arteriosclerosis is quantitatively related to the clinical manifestations of coronary heart disease. In Blumgart and Schlesinger's very beautiful injection studies it was clearly shown that, in the presence of clinical coronary heart disease in the form of angina pectoris or myocardial infarction, the coronary arteries at post-mortem examination show extensive arteriosclerosis, a degree of arteriosclerosis definitely *in excess* of that found in

patients without such clinical disease. This is so despite the fact that *essentially all so-called "healthy" individuals* show some degree (and often a marked degree) of coronary arteriosclerosis. The important issue is not that the apparently healthy individuals do show *some* coronary arteriosclerosis, but rather that they show a lesser extent of this process, on the average, than do those individuals with overt clinical coronary heart disease. In a careful study of post-mortem material from individuals dying in the age range from 26-40 years of age, Spain showed clearly that the average degree of narrowing of the coronary arteries due to accumulation of arteriosclerotic tissue in the intima was very much greater in individuals who died of myocardial infarction than in those who died accidentally of a variety of causes other than clinical heart disease

The studies of Dry, Edwards and White provided similar findings of an excessive degree of coronary arteriosclerosis in persons with clinically-manifest coronary heart disease. None of these findings call for an insistence that every case of clinical coronary heart disease, either in the form of angina pectoris, coronary insufficiency, or myocardial infarction, necessarily rests upon an etiology of coronary arteriosclerosis, although it is quite clear that the vast majority of such cases are significantly associated with coronary arteriosclerosis Some authors have considered coronary arteriosclerosis to be the etiology of as many as 95 per cent of cases of clinical coronary heart disease, while others have suggested somewhat lower percentages than this. Other possible pathological bases for clinical coronary heart disease have involved such features as (1) rheumatic or syphilitic involvement of the coronary artery ostia, (2) anomalous origin of one or more of the coronary arteries, as from the pulmonary arteries, and (3) anomalous congenital stenotic lesions of the coronary arteries This entire latter group of possibilities is regarded in present-day coronary heart disease material not to constitute anything more *than perhaps 10 per cent of the total* basis for clinical coronary heart disease. Thus it seems quite clear that coronary arteriosclerosis is the major underlying lesion present in the arteries related to the *development of clinical coronary heart disease*. However, this fact has created a certain amount of confusion in

the mind of certain investigators who doubt the etiologic significance of coronary arteriosclerosis and who misunderstand its relationship with the clinical disease. One such misconception is that which centers around the widespread occurrence of coronary arteriosclerosis in the adult population of a country like the United States

It is perfectly true that if one were to examine the coronary arteries of a large group of 50 year old United States males in health, one would find an appreciable average involvement of such arteries with arteriosclerosis. Indeed some of the individuals in apparent health will show a greater degree of coronary artery arteriosclerosis and attendant narrowing than will certain individuals of the same age and sex who have suffered one, two, three, or even four myocardial infarctions An erroneous conclusion that has been drawn by some is that coronary arteriosclerosis cannot be very important if individuals in apparent health can have, at times, more coronary arteriosclerosis than individuals who have overt clinical coronary heart disease. We do know now that, on the average, the degree of coronary arteriosclerosis is higher in individuals with clinical coronary heart disease than it is in otherwise comparable individuals without clinical coronary heart disease But what we must realize urgently is that individuals who are in apparent health today are fully entitled to show varying degrees of coronary arteriosclerosis, some very extensive degrees, some moderate degrees, and some *minimal* degrees. This in no way contradicts the relationship of coronary arteriosclerosis with the clinical entity, coronary heart disease.

First, it is important to realize that the individuals *in apparent health today* at age 50 years represent the prime substrate out of which grow the individuals who later become labelled "individuals with overt clinical coronary heart disease." Certainly if coronary arteriosclerosis is etiologically related to clinical coronary heart disease, it is essential that many so-called healthy individuals must be developing coronary arteriosclerosis, for otherwise we would never see any *new* cases of clinical coronary heart disease. This latter is unfortunately not the case, inasmuch as the clinical entity continues to develop in alarming proportions in our population every day. The true nature of the

relationship of coronary arteriosclerosis and clinical coronary heart disease is really that, with an increasing average degree of coronary arteriosclerosis, the *risk* of a clinical manifestation such as angina pectoris, coronary insufficiency, myocardial infarction, or heart failure becomes progressively greater. It is important to underline that this is a *risk* of such a clinical event becoming greater. It is *not* an absolute certainty nor is it an absolute certainty *in any specified time interval.* The matter might be put this way. If one were able to segregate two groups of individuals in the population, both groups being in apparent health, with one group showing an extensive degree, on the average, of coronary arteriosclerosis and the other showing a minimal average degree of coronary arteriosclerosis, and then could follow both groups for some time period, e.g., one month, one year, or ten years, the following would be true. There would be more cases of clinical coronary heart disease appearing in the group with extensive coronary arteriosclerosis than there would be in the group with minimal coronary arteriosclerosis. Furthermore, the wider the separation in average degree of coronary arteriosclerosis between the two groups the wider will be the disparity in numbers of individuals who develop a clinical manifestation of coronary heart disease in any particular time period.

Precisely why it is that one individual with a particular degree of coronary arteriosclerotic involvement has a clinical episode at some period in life and another avoids such an episode for some extended period beyond that is not at all clear at the present moment. It is entirely possible that this will not be clear for many, many years to come. Speculation is, of course, easy as to possible reasons for the sudden transformation from the sub-clinical state to the clinically overt state of coronary disease. For example, the occurrence of thrombosis superimposed upon an arteriosclerotic area occurring over a period of hours and days can effect this transformation The occurrence of intimal hemorrhage into an atheromatous plaque and the changes attendant upon this can suddenly decrease blood supply critically to a region of the myocardium and produce clinical manifestations. In addition, physiologic factors operating in an individual with narrowed coronary arteries can conceivably be immedi-

ate provoking factors. The extent to which such factors as functional vascular spasm are operative is not clear but one should not rule out their possible importance. One issue must remain uppermost in the mind of the physician dealing with the problem of coronary heart disease in a preventive manner, namely, that with increase in the degree of arteriosclerotic narrowing, the risk of a clinical episode rises progressively. This is so even though no date can be assigned to such an episode nor may we know what immediate factor will precipitate the clinical episode. In problems such as these it is often worthwhile to reflect upon our medical objective. In this case our objective is the prevention of *clinical* coronary heart disease While understanding of every last facet of the physio-pathology of the evolution of coronary heart disease is a most desirable and laudable aim, this should never be allowed to interfere with efforts to reduce mortality as soon as possible whether or not the entire physio-pathology is understood The entire body of evidence on this subject would indicate that if coronary arteriosclerosis could be minimized, the incidence of and mortality from, clinical coronary heart disease would also be markedly reduced This is the essential issue here That confusion on this issue is rife in high places can best be illustrated by citing certain important studies which have attempted to cast doubt on the importance of coronary arteriosclerosis for clinical coronary heart disease. In one such study, Morris[16] has obtained data from pathological records in one large London hospital where he felt the pathological grading scheme was sufficiently similar throughout a period of 40 years to enable him to estimate whether coronary arteriosclerosis exhibited a rising trend, a falling trend, and or no change over this time period His finding in the material at his disposal from autopsy records was that coronary arteriosclerosis appears to have decreased in average degree over this 40 year span in England However, during that same span of years the vital statistics for England showed that there appeared to exist a real and striking increase in the incidence of clinical coronary heart disease and in mortality therefrom, even after correction for medical awareness of the disease and for improvement in diagnostic methods. When such a situation arises there are several

possibilities that must come into consideration. But one point, both of philosophical and scientific consequence, must first be emphasized. Whatever possibilities are invoked to explain the paradoxical findings, they can hardly be correct if they flout directly other existing well-established, observational data. At any time the existing *interpretation* of solidly-established observational data may require revision, even radical revision, but new facts brought to light on an issue cannot negate *facts* which have also been proven to be as solidly established. Some of the possible explanations of the observations of Morris concerning the apparently opposite trends in coronary arteriosclerosis in England and those in clinical coronary heart disease mortality are the following:

First: Is the pathological grading that has been used *really* on a constant basis, such that one can use the reports of pathologists of even one hospital over a 40 year period for this type of analysis?

Second: Is the clinical material of the Guy's Hospital on which these conclusions are based really representative of the trends in the British population-at-large? With respect to this issue one might appreciate better assurance of the representative character of such hospital material. Physicians are well aware that numerous factors, even some over and above the type of illness which results in hospitalization of particular types of patients can change markedly from one decade to the next Indeed, they can even change from one year to the next, depending upon the introduction of new therapeutic and diagnostic tools The issue of comparability of hospital material over a 40 year period in a particular London hospital is a real and major one

Third: One may assume that the possible objections inherent in the first and second questions raised above are not valid and that the data are as they seem to be. Then the problem can be stated, "Are these the only data we have on this subject or are there other?" In the text above are very crucial solidly-established experimental data relating coronary arteriosclerosis to clinical coronary heart disease. Hence, we are not operating in a vacuum with respect to this problem, for we have excellent direct evidence that coronary arteriosclerosis is indeed related to

clinical coronary heart disease. No data accumulated by Morris or by others concerning arteriosclerosis trends over 40 years in London hospitals or coronary heart disease mortality in Britain over that same time period can possibly negate these well established relationships. If the observations detailed by Morris are truly correct as they stand, there must be some rational way to bring them into harmony with the known, well-confirmed relationship of coronary arteriosclerosis and clinical coronary heart disease. We know well that we do not understand all the factors that convert a sub-clinical case of coronary arteriosclerosis into a case of clinical coronary heart disease. This has just been alluded to repeatedly. Therefore, it would be very pertinent for us to inquire whether one or more of the factors that determine the conversion of coronary arteriosclerosis at the sub-clinical level into clinical coronary heart disease might not have undergone alteration in this 40 year period in England and thus be responsible for the trends observed. Indeed, with this approach one might hope that the resolution of this apparent paradox would add additional understanding to the entire problem of coronary heart disease rather than serve merely to confuse the issues. For some reason the type of data uncovered by Morris has been used by some authors and some so-called authorities on coronary disease as evidence refuting completely a host of other relationships, such as the relationship of pathologic to clinical findings, such as the biochemical relationship of blood lipids with coronary heart disease, and still others. These last mentioned relationships can in no way be contested by the type of evidence which Morris has presented, since the relationships stand on their own merits. It is indeed discouraging with respect to the progress in understanding disease that data such as those of Morris are misinterpreted and misused.

Other aspects of the relationship of coronary arteriosclerosis with clinical coronary heart disease have been equally misunderstood and misused with the result of adding confusion. A cardinal one that deserves discussion is that of the relationship between coronary artery disease in the male and the female of the human species, both with respect to the pathological features of coronary arteriosclerosis and with respect to the occurrence of

clinical coronary heart disease. The best available data indicate that the following is true for young men and young women, for example, *in the 30-39* year age decade: (1) there is, on the average, a greater degree of involvement of the coronary arteries with artriosclerotic narrowing in the men of this age group than there is in the women. (2) There is a much greater incidence of the occurrence of clinical coronary heart disease in men of this age group than in women. The exact extent to which the incidence in men exceeds that in women has been estimated to be anywhere from two-fold to twenty-fold, depending upon the authority quoted. Many of the authoritative comments on this subject are based upon material with a variety of biasses built in and hence can be disregarded entirely. It does appear however from vital statistics information that probably the correct order of magnitude of this factor of difference is about 4 or 5, that is, *men in this age decade have about 4 or 5 times as great an* incidence of clinical coronary heart disease and death therefrom as do women in this same age decade. On the other hand, the difference in the average degree of coronary arteriosclerosis between men and women of this age decade is by no means a 4 or 5-fold difference. It is a very much smaller difference. Some authorities have concluded that since the incidence of clinical coronary heart disease is about 4 or 5 times as great in the male as it is in the female but since the difference in degree of coronary *arteriosclerosis is very much less than this, there must exist* some reason why males are so much more susceptible to coronary heart disease than females, other than the factor of coronary arteriosclerosis. This type of argument is based on the *assumption* that if the clinical incidence of coronary heart disease is 5 times as great, the amount of arteriosclerosis must necessarily be 5 times as great in men than in women. A search of any of the elements of simple logic, a search of the literature, or any other available source will reveal no evidence whatever for the expectation that the difference in degree of coronary artriosclerosis between men and women must be 4 or 5 fold if the difference in clinical disease incidence is 4 or 5 fold No one has ever shown that these two related phenomena must necessarily be associated *by a straight-line relationship.* Indeed a variety of

biological phenomena, physical phenomena, and others are known not to be related in this linear way. A simple analogy would be that between the radius of a circle and the area of a circle. If the radius of a circle is doubled, the area is increased four-fold. It is highly unlikely that anyone measuring the area of circles of these two radii would express surprise that the area of the circle drawn from a radius twice as large as that of the first circle is found to be four times as much instead of two times as much. Why surprise is expressed concerning the absence of a linear relationship of coronary arteriosclerosis with clinical coronary heart disease is not at all clear, except insofar as it is a manifestation of loose scientific thinking. It should *occasion no* surprise if the final evolution of the facts would indicate that a *ten per cent increase* in degree of arteriosclerosis above a particular value might result in a two-fold, four-fold, or even six-fold increase in the risk rate of an attack of clinical coronary heart disease. This may very well turn out to be the case. Such variables need not be associated in a straight line relationship. Were this simply a matter of erroneous thinking with no consequences, one would hardly need to labor the point further. But the absence of the *straight-line* relationship between coronary arteriosclerosis and clinical coronary heart disease incidence has led some persons to state that the two phenomena *must* not be related at all, although all the evidence clearly *proves that they are*. Also, and perhaps more damaging, it has led to the concept that since coronary arteriosclerosis is not adequate to explain the difference in incidence of clinical coronary heart disease between the male and female, it is necessary to look for some other factor of explanation. As a result of such erroneously-based thinking, vast research projects can be initiated to uncover this hypothetical other factor which it is *deemed* necessary to discover to account for the male-female difference. It is not the intent here to state that no other factor could possibly exist, but rather to state very clearly and unequivocally that if fallacious reasoning leads to a search for some other factor presumed to be necessary, then such a search may very well be a wild goose chase leading to a non-existent pot of gold at the end of the rainbow.

There is another major area where misunderstanding of

the relationship between coronary arteriosclerosis and clinical coronary heart disease has delayed adequate progress with respect to the practical aspects of management of this disease. It is a very well-known fact to every physician that no method exists at the present time for an anatomical or microscopic examination of the coronary arteries during life to determine the exact degree to which they have been narrowed by arteriosclerosis. Nor does there exist any other technique which will enable one to assess the exact degree of such arteriosclerosis. For inexplicable reasons, statements repeatedly appear in the medical literature to the effect that since no method exists for measuring the degree of coronary arteriosclerosis during life, there is nothing that can be done with the problem of *clinical* coronary heart disease until such measurements are available No scientific evidence can be marshalled to support such a statement. If certain biochemical and physiologic *variables can be quantitatively related to the* incidence of clinical coronary heart disease, our inability to measure the degree of coronary arteriosclerosis in life simply has nothing whatever to do with prosecution of any of the leads that arise out of the measured relationship between the biochemical and physiologic variables and the phenomenon of clinical coronary heart disease. This important issue can be further illustrated *by taking an extreme point of view. Let us assume* (*even* though the assumption is false) that arteriosclerosis of the coronary arteries had nothing whatever to do with clinical coronary heart disease. There still would exist every reason to go forward rapidly with the study of bio-chemical and physiological variables in relation to the clinical entity, even without knowing the underlying pathology at all This is not to say that knowledge of the underlying pathology and the relationship of bio-chemistry to the pathology as well as to the clinical entity is not desirable. Of course it is an ultimate goal sought by all students of this disease. An excellent illustration of the danger of impediment to practical progress with management of coronary heart disease arising out of the erroneous impression that we must wait for a method of measurement of coronary arteriosclerosis during life is available in the field of the relationship of blood lipids with coronary arteriosclerosis and clinical coronary heart disease This

relationship itself will be elaborated on in detail in subsequent chapters. At this point it is sufficient to state that a strong relationship exists between blood lipids, in the form of lipoproteins, and clinical coronary heart disease.

Those who argue the immediate need to be able to measure the exact degree of coronary arteriosclerosis in life say, "Since the blood lipids operate via an effect on degree of coronary arteriosclerosis, and since we cannot measure exactly how much coronary arteriosclerosis there is in life, how can we possibly apply the blood lipid findings clinically?" The answer to this is that the blood lipid findings have been developed in relationship with *clinical* coronary heart disease. They do not rely in any way, for support, upon any findings having to do with coronary arteriosclerosis. Neither is the utility of this relationship in the practical management of prevention and treatment of clinical coronary heart disease in any way dependent upon a relationship of the blood lipids with coronary arteriosclerosis or upon any hypotheses concerning such a relationship. It is true that most workers who have studied this problem feel the evidence is extremely strong that the relationship of blood lipids with clinical coronary heart disease does arise via the intermediacy of coronary arteriosclerosis, but this is in no way necessary. Should it turn out in the future that the blood lipids are in *no* way related to coronary arteriosclerosis, the well-established relationship with clinical coronary heart disease would be *just as useful* and just as applicable in the problem of prevention and management of coronary heart disease. Ultimately of course one would like to know the interrelationship of all these measures and entities, but it is very important not to confuse *supposed* dependency upon one unmeasurable variable with the ability to go ahead with the problem at the clinical level. Therefore, the inability to measure degree of coronary arteriosclerosis in the living person need not in any way be a stumbling block to progress with the practical problem of prevention or treatment of *clinical* coronary heart disease. It is in an area such as this that it is extremely important to differentiate clearly what is meant in discussing coronary arteriosclerosis, and what is meant in discussing clinical coronary heart disease.

From the point of view of the physician interested in trying to prevent clinical heart disease, from the point of view of the intelligent layman who would like to avoid coronary heart disease, interest centers in the *clinical* entity of coronary heart disease, in manifestations such as myocardial infarction, angina pectoris, arrhythmias, heart failure, and death. The interest is not primarily in the pathological process underlying such clinical states. To be sure, where understanding of the pathology could assist with the management of the problem at the clinical level, such understanding is greatly to be welcomed. However, since the essence of the problem at the practising physician's level is clinical coronary heart disease rather than pathology, it is the intention of the author of this book to develop completely in the ensuing chapters the concepts of interest for clinical coronary heart disease without any *dependence* whatever upon concepts of coronary arteriosclerosis. Where it is felt that coronary arteriosclerosis represents the mechanism by which a given effect is mediated, comments will be made to so indicate, but in no case will the development of the ideas and the application of such ideas be in any way dependent either upon facts or concepts concerning coronary arteriosclerosis. Rather, the intent is to develop for the physician reader what we know about the evolution of coronary heart disease as a clinical entity, what can be done about its advance prediction, and what can be done about its prevention and management, without any dependence upon its inter-relationship with coronary arteriosclerosis.

Chapter II

IDENTIFICATION OF FACTORS IN THE DEVELOPMENT OF CORONARY HEART DISEASE

THE SUB CLINICAL phase of coronary heart disease is that upon which major interest must center for real effectiveness in the prevention of the clinical disease *Prevention* of clinical coronary heart disease appears to have more attractive prospects than does treatment of acute clinical episodes when they arise By the very nature of the statement that coronary heart disease is sub-clinical during that period when its recognition is most urgent the inference is made that it will be necessary to develop some means of identification for *individuals* which will determine the status with respect to sub-clinical coronary heart disease. Stated alternatively, an endeavor is necessary to develop variables that can be measured which will provide some way of rating a person on a scale of risk with respect to his future prospects of evolving from the sub-clinical phase into the phase which must be avoided, namely, the phase of clinically manifest coronary heart disease. In such an endeavor one would be perfectly justified in considering any possible measurement that can be made in people, where the term might refer to measurements in the area of anatomy, of physiology, of biochemistry, of psyche, of family traits, of environment, or even still other areas It could not be predicted in advance in a totally new problem from which of these areas the significant information might arise If no information is available on this problem, one can simply screen measurement after measurement to determine whether or not any provide information concerning either the rate at which sub-clinical coronary heart disease is developing or its total extent. Quite obviously such a screening procedure could be extremely lengthy before

any variables of consequence are uncovered. *Unfortunately this* may be necessary in certain problems. In others there exist some available clues suggesting profitable directions of investigation. *At times such* clues may have arisen from animal experimentation. At other times they may have arisen through the practical clinical experience which has been accumulated over a period of years and suggests that one or another factor might be of importance. In the absence of either of these sources of possible leads, to avoid the massive screening procedure one might, from a knowledge of the pathology of a disease or from some wholly other facet, such as the inter-relationship between two diseases, get some idea of a profitable area in which to seek clues rather than to screen every possible area.

It is worth comment here upon the nature of measurements *that can be made. Measurements fall into various categories* depending upon the precision and accuracy with which they can be made. For example, with respect to the height of a man, one could measure this quite accurately and there would be no reason not to do so. On the other hand, with respect to some other factors characterizing an individual, one might be quite satisfied to be able to grade individuals into four classes, such as zero, plus one, plus two, plus three, and plus four There is nothing wrong with either type of measurement It is self-evident that where a measurement can be refined, it will in general be more useful in assessment of a trait of interest. However under certain circumstances, where a particular measurement is quite variable in an individual from day to day, or hour to hour, it would hardly be worthwhile expending too great an effort in obtaining *great precision on any single measurement, since such precision* is not warranted because of the variation with time A pre-requisite of any feature to be measured in individuals is that the feature be different in extent in those persons developing sub-clinical coronary heart disease at a high rate compared with those developing the disease at a moderate rate and different to an even greater extent from those developing the disease at a low rate It does not matter whether the measurement is *lower* in those developing the disease more rapidly than in those not developing the disease rapidly or whether it is *higher* In either event the

measurement will be useful for the present purposes. Next, it is essential that the measurement which is different for those developing coronary heart disease rapidly from those developing it at a lesser rate must be different *early enough* in the sub-clinical phase of the disease to be useful. This requirement deserves an illustration For example, if there were a measurement related to coronary heart disease that became abnormally high or abnormally low in the couple of hours or couple of days preceding a myocardial infarction, such a measurement would be of very little use with respect to minimizing the rate of development of sub-clinical coronary heart disease, which goes on for a period of years and decades. To be really useful the measurement must be abnormal early in the period of sub-clinical development of the disease, which means it must characterize the individual years, if possible, before the occurrence of a clinical *manifestation* of coronary heart disease, such as myocardial infarction

Another very important feature to be determined for each such measurement is the extent to which that measurement provides new, additional information concerning the problem at hand, in this case the rate of development of sub-clinical coronary heart disease It is entirely possible that in approaching a problem such as coronary heart disease one might find that not only is there one measurement of importance, but there are as many as five or more measurements that can be shown to have some relationship to the rate at which sub-clinical coronary heart disease is developing In the event that multiple measurements seem valid, it is of prime importance to determine whether or not all the measurements provide what may be called *independent*, or truly new, information If each measurement does provide independent information, then it is necessary to measure each in order to obtain the best assessment of the rating of a particular person with respect to sub-clinical coronary heart disease If the measurements do *not* all provide independent information, then the measurement of any which do not provide *independent* information is *superfluous*, confusing, and a waste of time Let us consider a specific illustration concerning this feature of independence utilizing some factors for which evi-

dence exists of a relationship with the rate of development of sub-clinical coronary heart disease. These are the blood lipid level and a family history of early clinical coronary heart disease. Do these two factors provide independent *information that can* be used to assess a person's status with respect to coronary heart disease at the sub-clinical level? Assume that family history of coronary heart disease can be rated on a measuring scale from zero through plus 4, depending upon the frequency of occurrence of early coronary heart disease in parents and other relatives of the individual. It is known (to be developed in detail later) that blood lipid levels are related to the rate of development of sub-clinical coronary heart disease, the higher the blood lipid level, the greater the rate of development of sub-clinical coronary heart disease. In the absence of other information it is possible that the availability both of the family history rating and the blood lipid level may provide much more information than either one alone. *However, it is not necessarily true that availability of* both types of measurement allows a better assessment of the heart disease risk in an individual under study. In order for the two types of measurement to provide more information than either one alone, they must provide independent information, in other words, information concerning factors in development of coronary heart disease that are at least in part really basically different from each other. It might be imagined, for example, that a family history of early coronary heart disease could operate in one of several possible ways, such as inheritance of an anatomically peculiar coronary vascular tree that either favors poor nutrition of the heart muscle or predisposes to narrowing of the arteries by some mechanism, or inheritance of a variety of other possible anatomical or physiologic features affecting the coronary arteries or the heart itself. On the other hand, the unfavorable family history might conceivably reflect a predisposition, on a hereditary or familial basis, to the development of elevated blood lipid levels. It should be evident that, if the family history operates only by influencing the chance that the person would have an elevated blood lipid level, the family history is then providing nothing additional to the information directly available in a blood lipid measurement. Indeed, under such circum-

stances, the family history would at best be providing far more crude information concerning the blood lipid levels than blood lipid measurement itself. In such a case one would consider that the family history provides no independent information and hence that a rating on a family history basis would contribute nothing new if the blood lipid levels are available. On the other hand if it should turn out that the family history really operates via some mechanism such as inheritance of a poor coronary vascular tree anatomically, then the situation is an entirely different one. In this event, the family history does provide additional, independent information and hence an individual's risk of development of coronary heart disease is much better assessed if both the family history and blood lipid measurements are available than with either measurement alone. Another way of presenting the problem of independence of information would be along these lines. Assume that several factors were measurable and proven to be associated with the development of coronary heart disease. Assume further that two individuals had the same value of each such factor If now a new measure becomes available, and the two individuals differ on this measurement, then is the risk of coronary heart disease higher in one of the individuals than the other? If the risk is higher, the new measure does provide independent information and should definitely be added to the battery of evaluation tests. This is essentially the scientific basis for testing independence of information provided by measurements There exist excellent statistical methods for checking the issue of independence, such methods being based in essence upon the procedure of making all but one factor out of a set of factors equal and then testing for the association of the remaining single factor with the disease in question When by such a careful statistical test the one factor still seems related to coronary heart disease, it can be inferred that statistical independence has been demonstrated Such demonstrations of statistical independence, or demonstrated Such demonstration of statistical independence, or respect to coronary heart disease is very far from an academic matter First of all, it is of tremendous importance with respect to guiding further research efforts with respect to the disease. Second, at the practical clinical level it can help avoid duplication

of effort and of tests and indeed can help avoid erroneous and serious mis-diagnosis and mis-prognosis of the future of some individuals. Thus, returning to the illustration of family history and blood lipids, let us assume that by the statistical test methods referred to above it has been demonstrated that the blood lipids are important but that the family history is of importance only because, on the average, *the blood lipids are higher in those families* where coronary heart disease has occurred excessively. In this case there is no independent information in the family history. Now, if a clinician dealing with a particular patient does not realize this fact, he can make errors in either of two directions. First, in a patient whose blood lipid status and whose family history are known, and in whom the blood lipid status is excellent but the family history is poor, this physician, not realizing the lack of independent information in the family history, might erroneously be concerned about the unfavorable family history. The correct point of view in such a situation is that, even though *on the average the blood lipids may be worse in persons with a* bad family history of coronary heart disease, this particular patient seems to have escaped the blood lipid defect and need have no fear whatever concerning the poor family history of coronary heart disease with respect to his own outlook for development of this disease. The error that can be committed on the other side occurs in the case of a person who has an excellent family history of longevity and freedom from coronary heart disease but where the person has extremely high blood lipid values The extremely high blood lipid values would indicate a high risk of future clinical coronary heart disease and a high rate of development of the entity of sub-clinical coronary heart disease The prognosis is therefore unfavorable If the physician assumes in such a case that the patient has nothing to fear because he has such an excellent family history of freedom from coronary heart disease, he would be giving the patient a very false sense of security unjustified by the facts This might even prevent the patient from taking necessary measures which would reduce his *high risk of future coronary heart* disease. These illustrations are presented primarily to point up the intense practical clinical importance of knowing whether or not the various factors meas-

ured truly provide information of independent character. There is one special situation that must be considered before too casual a dismissal of the independent importance of a particular factor with respect to coronary heart disease. A particular factor that is known to be associated with coronary heart disease may make its effects manifest at one period of life whereas it does not do so at some other period in life. Let us return again to the illustration concerning blood lipids and family history of coronary heart disease. In testing for independence of family history of coronary heart disease and blood lipids, one would apply the types of technique discussed above. However, the possibility has to be considered in this situation that the nature of the familial factor is such that it makes itself manifest, for example, at some relatively later period in life than early adulthood One might consider the possibility, that a poor family history *is associated* with a predisposition to poor blood lipid control, but that this predisposition does not become *manifest* in the average person until 35 or 40 years of age. If an individual at 30 years of age is under consideration and if his blood lipids are found *to be* favorable but his family *history* poor, the finding of the favorable blood lipid pattern at age 30 years *would* lead, by too casual dismissal of the family history, to the concept that family history is unimportant for this individual. However if the familial predisposition is of a type becoming manifest between 35 and 40 years of age, the family history should not be dismissed. Instead in this type of individual with favorable blood lipids at 30 years of age, the family history should put the physician on notice that the future blood lipid status of this patient should be watched In this hypothetical illustration, though the family history is operating via an effect upon blood lipids, it is providing independent information in that it tells us that the blood lipids may become abnormal *in this person* at some later time in life whereas this might not be the case in the population-at-large without this particular familial predisposition. This might be regarded as an illustration of *semi-independent* information, and hence information that should *not* be disregarded Probably this type of situation arises relatively infrequently Nevertheless we know that it can arise and should be borne in mind in evalua-

tion of the approach to factors involved in a disease such as coronary heart disease.

In summary our goal is to identify each and every factor, if there are indeed multiple factors, which provide independent *information concerning the outlook for the development* of sub-clinical and ultimate clinical coronary heart disease. For if these independent factors can be identified, we can make the best *composite assessment* of a person's status and further can utilize the possibility of a multi-faceted approach to prevention of heart disease in an individual. And the possibility of a multi-faceted approach needs to be considered. If there is *only one* factor involved, then there is no indication for a multi-faceted approach. On the other hand, if multiple independent factors really do exist, they must of course all be given attention. There may exist a difference in the ease with which one factor or another can be brought under control and it would certainly accrue to the patient's benefit to control those factors readily controllable than not to manage any of them effectively Of course, where multiple factors exist, control of all can be anticipated to produce the best clinical results in reduction of risk of heart disease.

The entire issue of independence of factors involved in the development of coronary heart disease is of great pertinence to the research worker as well as to the practising clinician. From clinical evidence, from epidemiologic studies, from endocrine studies, and from a variety of other sources new information possibly pertinent for the problem of coronary heart disease has arisen and will arise in the future. It is urgent that when such new information arises, the first question to be asked is, "Does this really provide *new*, independent information in terms of factors that are related to the development of clinical coronary heart disease?" This does not infer that the information itself is not new, but rather the question is being raised here as to whether the information is but another reflection of some factor which we already know about and concerning which cognizance is already taken. As an illustration, it may be assumed that new research suggests that the level of a particular hormone is either lower or higher in those individuals developing sub-clinical coronary heart disease at an excessive rate Assuming that this find-

ing had never been made before, it is obviously a "new" finding. Indeed it may be a finding of tremendous importance in our understanding of the disease as well as in our handling of it, but it is of prime urgency to know how this hormone level operates. For example, if the particular hormone under consideration operates as one factor in the control of the level of blood lipids, it is vital that this be realized. For there would be no virtue in attempting to alter that hormone level if the particular patient already has favorable blood lipid values. In this type of situation the purpose of an effort to alter the level of this hormone would be only to attempt to achieve an improvement of the blood lipid level This in no way minimizes the importance of the particular hormone, but it may save the patient and physician needless effort to alter something of no consequence of and for itself If for example one already were able to alter the blood lipid level very favorably by simple methods not involving this particular hormone, it would follow that there is no additional benefit conferred upon the patient by the alteration of the particular hormone system for itself In the problem of coronary heart disease as with other problems of this type in medicine, we must endeavor to achieve a reduction to simplest terms consistent with the reality of the situation If the simplest terms involve the consideration of ten separate independent factors, we have no choice but to deal with all ten On the other hand if the simplest terms involve one or two factors, it is confusing and a waste of effort to retain eight or nine additional duplicative factors that truly have no independent position with respect to acceleration of the disease process under consideration.

THE IDENTIFICATION OF INDEPENDENT FACTORS ASSOCIATED WITH THE DEVELOPMENT OF SUB-CLINICAL CORONARY HEART DISEASE

It was stated above that in a new problem one could approach the search for factors related to the development of the disease by screening processes, screening every possible anatomical, physiological, and biochemical value, or one could, alternatively, utilize leads that arise through a variety of sources. In the case of coro-

nary heart disease we have been abundantly presented with leads suggesting factors to be investigated. It may be pertinent at this point to list some of the numerous leads that investigators of the problem of coronary heart disease have had available to them and the sources from which these leads came. It is of interest to remark, however, that the entire list of leads have so far produced only two factors that appear to be independent ones related to the acceleration of development of coronary heart disease at the sub-clinical level. At the present time all the others seem very likely to be related to one or another or to both of these two factors.

These leads are listed below:

(1) The greater frequency of occurrence of episodes of clinical coronary heart disease with increasing chronological age.

(2) The greater frequency of occurrence of clinical coronary heart disease in the male of the human species as compared with the female especially at relatively young ages.

(3) The occurrence of excessive and premature coronary heart disease in certain families characterized by blood lipid disturbance.

(4) The occurrence of premature coronary heart disease in diabetics at least in the pre-insulin era and the transition era.

(5) The similarity of the blood lipids to those in the arteriosclerotic plaques of the coronary artery.

(6) The induction of arteriosclerosis by cholesterol feeding in a variety of animals

(7) The difference in geographic incidence of coronary heart disease as determined by epidemiologic studies

(8) The implication of the diet of certain peoples in development of coronary heart disease.

(9) The change in incidence of coronary heart disease during privation, as in war years and post-war periods.

(10) The frequent association of coronary heart disease with hypertensive disease

(11) The occurrence of excessive arteriosclerosis in areas of the vascular tree subjected to excessive pressure.

(12) The excessive incidence of *coronary* heart disease in cigarette smokers.

(13) The excessive heart disease mortality in overweight persons.

(14) The widespread opinion that a family history of excessive vascular disease is a predisposing factor to coronary heart disease.

(15) The rising trends in mortality from coronary heart disease in the past half century in Western civilization.

(16) The striking relationship of xanthomatosis with coronary heart disease.

(17) The association of coronary heart disease with certain other diseases such as nephrosis and myxedema.

(18) The difference in coronary disease incidence for various occupational categories.

If coronary heart disease truly had some 15 to 20 independent factors involved in its development, the medical task of prevention and management would certainly be complicated and difficult. But 15 or 20 clues do not necessarily mean the existence of 15 to 20 independent factors in the disease. The first step is a *determination* of the validity of the information in the clue. Next, valid information *derived from* each clue must be assessed for its independence. At the present time, of all these clues and suggestions concerning coronary heart disease, *two major* factors have stood the test of careful analysis as being capable of providing valid *independent* information about the development of subclinical coronary heart disease and, of course, of ultimate clinical coronary heart disease. All the others appear to derive validity through a relationship with one or another of these two factors or with both. Therefore, the considerations immediately ahead deal with these two factors. The later chapters of this book will deal with the relationship of the other clues and suggestions to these two factors. It is not meant that the two factors to be described here are the only two that will ever be discovered to have independent status, or that other factors are either not valid or of importance. Validity and importance are issues of a different type from that of independence of information.

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highly recommended and while the findings derived therefrom often provide excellent leads for study of the human problem, the ultimate evidence with respect to blood lipids or any other factor must be derived in *the human population* directly. We must remain cognizant of the marked differences in the various animal species and of the possibility that what is important for one animal species may not hold for another. Indeed what may be important for *several* lower animal species may not hold for the human. Therefore while no thought should be given to the idea of deprecating results on coronary disease in the chicken, the rabbit, or the dog, it is still true that our interest is coronary heart disease in the human. Therefore any findings that must go into the day to day practice of clinical medicine in the effort to prevent coronary heart disease must have been proven valid for the human. This generalization holds for blood lipids or any other factor of interest.

How is the problem approached of demonstrating whether or not a factor such as the blood lipid level is associated with the development of coronary heart disease? Secondly, and beyond the question of association, is the measurement of blood lipids of practical clinical utility in determination of the rate of progression of sub-clinical coronary heart disease and hence in prediction of the most likely candidates for future clinically-manifest coronary disease? Even though some of the clues that lead to the study of blood lipids arise out of pathological considerations of coronary arteriosclerosis, the development of the evidence concerning blood lipids in clinical heart disease can and will be made wholly independent of any consideration of pathology. The reason for doing this was adequately explained in the previous chapter. It is not that the pathology is unimportant, it is not that we cannot learn from pathology, but inasmuch as our direct and practical concern is with the entity at the clinical level, it is important that any case made for blood lipids and their relationship with coronary heart disease be wholly independent of any of the pathological considerations. In this way numerous questions, criticisms, and doubts can be resolved immediately, since there is no dependence whatever on any pre-conceived

THE GENERAL PRINCIPLES INVOLVED IN TESTING FACTORS FOR RELATIONSHIP WITH CORONARY HEART DISEASE

In the evaluation of the significance of such factors as blood lipids and blood pressure in coronary heart disease, certain highly important general principles are involved, principles that can be utilized profitably in similar problems both with respect to other factors in coronary heart disease, and with respect to factors related to any disease. Such principles can be readily understood by combining their general features with a specific illustration of their practical clinical application, utilizing in this case blood lipids in coronary heart disease.

The suggestion that lipids of the blood might be associated with the development of coronary heart disease is a very old one, which comes to our attention from a variety of types of evidence. Listed previously were several of the areas of suggestion that the lipids of the blood might be important. Among these are experimental induction of an arteriosclerotic lesion in animals by the feeding of cholesterol, the finding that the lipids in the arteriosclerotic lesion are closely similar to the lipids of the blood, the excessive incidence of coronary heart disease in families with xanthomatosis or with blood lipid disturbances, and the excessive incidence of coronary heart disease in diabetics, at least in the pre-insulin era at which time many diabetics were frequently characterized by markedly elevated blood lipids. These are all but clues, falling short of provision of the direct answer concerning the role of blood lipids in the development of coronary heart disease in the population-at-large. It is precisely this group with whom we are concerned, since the overwhelming number of cases of coronary heart disease arise out of the population-at-large. If the blood lipids were of consequence only for relatively special categories such as the individuals with xanthomatosis, they would hardly be of much merit or significance with respect to the real problem of coronary heart disease, which goes vastly beyond that of coronary disease in a highly special group of individuals such as xanthomatotic subjects. Furthermore, while the use of experimental animals, such as the rabbit, the chicken, the dog, the rat, or the monkey for studies of arteriosclerosis is to be

such factors as age, sex, etc.) but free of evidence of clinical coronary heart disease. The presumption here is that, while coronary heart disease is developing to a greater or lesser extent in those free of *overt* clinical disease, on the average these individuals have a lesser degree of the disease and have been developing it at a slower rate than those of the same sex and age group who have already presented clinical signs and symptoms of coronary heart disease This presumption is actually closer to a definition, for if *clinical* coronary disease is the problem at hand, it is obvious that those who manifest it have more of it than those who do not This represents one valid manner of approaching such a problem However, there do exist certain fundamental objections to this approach alone. First the measurements in those persons with clinically-manifest coronary disease are being made *after* overt signs and symptoms are present. Therefore it is impossible to know at what point in such a person's life any proven abnormality in blood lipids had appeared For utility in the direction of the ultimate objective of early interruption of sub-clinical coronary disease it is essential that the blood lipid factors under study be abnormal early in the *sub-clinical phase.* The study of persons with manifest coronary heart disease does not provide any way of knowing whether a factor (such as blood lipids) became abnormal shortly before clinical signs or had been abnormal many years before Indeed there is even a more dangerous possibility namely that the lipid abnormality appeared *after* the onset of clinical signs and symptoms either spontaneously or as a *result* of the clinical episode. If this possibility were a reality, the information would be useless for the purpose we have in mind, namely using the measurement of such factors to evaluate and rank people during the sub-clinical phase of coronary heart disease Even if the abnormality of the measurement appeared a very short time *before* clinical signs and symptoms, the usefulness of the information would be extremely limited for purposes of identification of high-risk candidates and for the institution of preventive measures. Why, then, should one consider at all the measurement of some variable such as blood lipids in subjects with *overt* coronary disease in the effort to evaluate possible factors involved in its development? The

notions concerning the interrelationship of coronary arteriosclerosis with sub-clinical and clinical coronary heart disease.

Thus, the problem at hand is an evaluation of the blood lipid factor in the evolution of coronary heart disease as a clinical entity, rather than as a pathological entity. However, our concern is mainly with the *sub-clinical phase* of the clinical entity. The type of study needed must bypass any pathology considerations and go directly to possible relationships between blood lipids and clinical development of coronary heart disease, either in its sub-clinical or manifest phases. *If blood lipids do represent a factor* in the development of clinical coronary heart disease, there must be *some* difference between the blood lipids of those humans with coronary heart disease and those humans without coronary heart disease. Or, if we regard coronary heart disease as a graded phenomenon, rather than a "yes or no" phenomenon, then there must be a progressive difference in the blood lipids as one passes from individuals with a low degree, or rate of development, of coronary heart disease to those with a higher degree, or rate of development of this disease. It is of no moment whether the blood lipids be higher with increasing degree of disease, or lower with increasing degree of disease, but there must be a *difference* in blood lipids in passing from those persons with less disease to those with more disease, or those developing disease slowly in *contrast with those developing disease rapidly*

THE CHOICE OF SUBJECTS FOR STUDY

Evaluation of the relationships of blood lipids with coronary heart disease requires availability of some way to grade the degree of disease or the rate of development in the subjects studied. But, as was mentioned earlier, no direct method exists to measure the degree, or the rate of development, of sub-clinical coronary disease, which is precisely what we would most like to measure. Two alternative choices suggest themselves

(a) *Comparison of blood lipids* in a group of subjects with documented manifest clinical coronary heart disease (in the form of angina pectoris or myocardial infarction) with the blood lipids in a group of *subjects otherwise comparable* (*with respect to*

ment of coronary disease could be identified by the blood lipid measurement at least 5 to 10 years before the transition to clinically overt disease. This type of evidence is precisely what is needed concerning sub-clinical coronary disease, free of the objection that the clinical episode itself may conceivably have produced the abnormal blood lipid level.

ASSOCIATION, PREDICTION, AND CAUSE AND EFFECT

When a variable, e g, blood lipid level, is measured in a disease entity such as coronary heart disease and in matched controls without overt heart disease and the mean level shows a difference between the two groups, whether higher or lower in the disease group than in the controls, it is possible to state that this variable is *associated* with the disease process. What the nature of that association is remains in any particular case to be demonstrated No clear-thinking scientist would ever claim that proof of association of a variable (such as blood lipids) with a disease (such as coronary disease) represents proof that the blood lipids are either *a* cause or *the* cause of the disease (such as coronary heart disease). But proof of association is the first step, and indeed a vast and major step forward This is an important issue, since misunderstanding of this differentiation has led some investigators to minimize the significance of proven associations between a measurement and a disease. Such investigators are prone to state, "All this proves is association, but it doesn't prove cause and effect." And with such a statement they blithely pass off as of little consequence associations of major and practical clinical importance

When an association has been proved between a measured variable and a disease, there are several possibilities that account for the association, among which are.

(a) The disease itself may cause the measured variable to be abnormal

(b) Both the disease and the measured variable may be affected by an underlying metabolic or other defect which is itself the true cause

(c) The abnormality in the measured variable may be the cause of the disease process

answer is the highly practical one that alternatives to this are very costly of time and effort and hence delay progress in understanding. The utilization of subjects with already-established clinical signs and symptoms of coronary heart disease is of great value as an *introductory* procedure to this problem, for subjects are available in great numbers, without the necessity of waiting for the clinical disease to develop in healthy persons. Because of the limitations just described (i.e., not knowing whether any blood abnormality did or did not precede the clinical event), it is imperative to supplement studies of groups with overt disease with additional long-term studies where the overt disease is permitted to develop out of a population in apparent health at their initial study. Thus, in the case of coronary heart disease, it is necessary to evaluate a variable of possible interest, such as blood lipid level, in a large sample of the population at a time when the persons involved are overtly well (which means that many are in various stages of *sub-clinical* coronary heart disease). The size of the population sample requiring study depends upon (a) the frequency with which apparently healthy people develop clinically overt coronary disease and (b) the time period over which the subjects are observed. A small sample observed over a long time period can usually yield the same information as a large sample observed for a short time period.

The value of such a study, should it reveal that those who later develop clinical coronary heart disease are either *higher* or *lower* in blood lipid level than the mean value for the population out of which they have grown, is that it has been shown that the blood lipid level is *different* for future coronary disease patients from that for the population-at-large *at a time when such persons are in the sub-clinical phase of the disease* For example, if a follow-up period averaging 1 year is utilized, then it would be known that the blood lipids are abnormal *at least* one year before the clinically overt disease is manifested If a follow-up period of 5 or 10 years is the average time period for the cases of coronary disease to grow out of the population, then it would be known correspondingly that the abnormality in blood lipids was present 5 to 10 years before overt symptoms and signs. Stated somewhat differently it would mean that sub-clinical develop-

ment of coronary disease could be identified by the blood lipid measurement at least 5 to 10 years before the transition to clinically overt disease This type of evidence is precisely what is needed concerning sub-clinical coronary disease, free of the objection that the clinical episode itself may conceivably have produced the abnormal blood lipid level.

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(a) The disease itself may cause the measured variable to be abnormal

(b) Both the disease and the measured variable may be affected by an underlying metabolic or other defect which is itself the true cause

(c) The abnormality in the measured variable may be the cause of the disease process

Ofttimes direct experimental choice among these three possibilities may be difficult, or even impossible. But this need in no way be discouraging, for there are many indirect ways to solve the practical problem even though the direct proof may be lacking concerning the nature of the association.

The three possibilities mentioned above deserve illustration and consideration with respect to the problem at hand, namely coronary heart disease.

The possibility that the disease itself is responsible for the abnormality in the measured variable in this case of blood lipids may be approached first. If one had discovered the abnormality of the variable in patients who had had a myocardial infarction, for example, it is possible to believe that the metabolic alterations attendant upon occurrence of a myocardial infarction might have themselves been responsible for the abnormality in the measured factor (e.g., blood lipids). However, this is precisely one of the reasons why one is not very satisfied with the discovery of an abnormal variable (such as blood lipids) in patients who have already manifested clinical myocardial infarction. This is also the reason for the need to do *prospective* studies where the bio-chemical measurements are made in individuals when they are in apparent health and where infarction or other clinical manifestations are then permitted to develop in a population of such individuals. The possibility would still exist even in the study of the sub-clinical disease to consider that the actual occurrence of the sub-clinical disease developing might be the cause of the abnormal lipid measurements. While patients developing sub-clinical coronary disease show no evidence whatever of an illness that might be suspected to lead to metabolic aberrations, the possibility cannot be ruled out that the disease itself is the cause of the abnormal lipid levels, although it certainly would seem much less likely than would be the situation wherein patients are studied in the already clinically manifest phase of coronary disease. Since the possibility cannot be ruled out, one must consider what the implications of such a prospect are. If, for example, identification of individuals with sub-clinical coronary disease is our objective and if the blood lipid abnormality were the *result* of the sub-clinical disease, this need not matter

in any way for our purposes. The results would be just as valid for purposes of identification of individuals developing subclinical coronary heart disease *whether* or not the disease caused the lipid abnormality. However, if our purposes are other than identification alone, then it would make some difference whether the disease causes the lipid abnormality. For example, if one were interested in the possibility that correction of the lipid abnormality would have some effect upon amelioration of the disease, the prospects would be dim if the disease *caused* the lipid abnormality The only conceivable way to determine this in the absence of direct information would be to make direct tests of the concept that decreasing the degree of the lipid abnormality in any way ameliorated the disease. If such tests showed a positive result, no further need would exist to raise the question of whether the disease caused the abnormality, since the objective itself, inhibition of the disease, would have been realized. In this sense, it is entirely appropriate to allow our objective to determine our course of action rather than to wait until some indefinite future for the direct proof of whether or not the disease causes the abnormality or the abnormality is one factor which causes the disease

The second possibility is that the disease and the abnormality are both the result of some other feature, be it a metabolic abnormality or some other property, rather than that the lipid abnormality is the cause of the disease, or the disease, the cause of the lipid abnormality One could visualize, for example, that a metabolic dysfunction such as that in the liver might in some way alter blood lipids and by some wholly separate mechanism might provide an effect upon the cardiovascular system leading to coronary heart disease While such a possible mechanism is not immediately obvious, it cannot be summarily dismissed In this case one might anticipate the possibility that alteration of the blood lipid factor (even though it has been proved to be associated with the development of coronary heart disease) might not slow the rate of development of coronary disease This possibility must be considered both with respect to prevention and therapy However, two points are to be borne in mind in such a case First, with respect to *prediction* of who is developing exces-

Ofttimes direct experimental choice among these three possibilities may be difficult, or even impossible. But this need in no way be discouraging, for there are many indirect ways to solve the practical problem even though the direct proof may be lacking concerning the nature of the association

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disease some 30 years ago, and as evidence accumulates it appears increasingly certain that his concept needs no appreciable modification

sive sub-clinical coronary heart disease, the possibility of a third factor being the cause of both the lipid abnormality and the coronary heart disease *is of no moment whatever.* For, all that is needed to achieve the requisite *predictive* information is the existence of a *relationship* between the blood lipids and the development of sub-clinical coronary heart disease, whatever be the cause of either one of them. Second, the hypothesis of a third cause is simply an hypothesis, based upon no facts. Unless *some facts develop in its favor, it is difficult to see why this more complicated* hypothesis is chosen by some individuals rather than the simplest one *directly* relating the abnormality of the blood lipids with the development of coronary heart disease. When one *chooses the simplest hypothesis, this does not mean that one insists* on the correctness of it, but rather that it *is* the simplest hypothesis and therefore deserves careful and intense evaluation to determine its truth or falsity. The actual practical evaluation of such an *hypothesis will of itself* provide *the best determination* of correctness. Certainly this is an approach far superior to the entirely unwarranted assumption that the simplest hypothesis must be wrong Here again the practical issue is paramount If one chooses to evaluate the simplest hypothesis that possibly the blood lipids may be a *cause* of coronary heart disease and follows up the implications thereof, namely, whether lowering or altering the blood lipids will alter progression of coronary disease, one may very *well achieve the tremendous clinical result which is* desired, namely, prevention or minimization of coronary heart disease The practical test itself will have laid to rest much of the need for consideration of possibilities of a more complicated relationship. *Until* and unless this extremely important possibility has been shown to be incorrect by direct clinical test thereof, it remains the most attractive hypothesis deserving of study For, in the case of blood lipids and coronary disease, one is led to this simplest hypothesis *not only by a strong set of data, namely,* association between the blood lipids and sub-clinical coronary heart disease, but also by massive indirect evidence which suggests that the relationship is truly a causal one. Anitschkow[4] suggested *the causal relationship between blood lipids and coronary heart*

exist as such circulating in the blood stream. Thus, even such a term as "free cholesterol" or "esterified cholesterol" is misleading since it tends to indicate or to suggest that these are two separate entities circulating *as such* in the blood. This is not the case. There can be demonstrated no evidence for any significant quantity of cholesterol circulating in the blood as such, or of phospholipids circulating in the blood as such, or of triglyceride circulating in the blood as such, or of fatty acids circulating in the blood as such. Instead all of these chemical constituents which comprise the lipids of blood are substructural units, or building blocks, for a series of very large molecules that do exist as such in the blood and which have been designated as *lipoproteins*. The designation, lipoproteins, simply implies the presence of structural entities in the blood comprised in part of lipid and in part of protein. The designation itself does not imply any specific protein or any particular lipid. Therefore whether cholesterol, cholesterol and phospholipid, or cholesterol, phospholipid, neutral fat, and fatty acid are all present in a particular lipoprotein is not the feature required to allow this definition or designation. If any one of the lipid entities is associated with protein to form a macromolecular structure, such a structure would be referred to as a lipoprotein. The lipoproteins are molecules of very large size, even the *smallest* lipoprotein being larger in size than a serum globulin molecule. The lipoproteins *are the* transport vehicles for the lipids in blood. Many investigators have commented on nature's need to solubilize the lipids in blood through the attachment of the various lipids to protein. Whatever the merits of this type of reasoning, it can hardly add anything to the statement that lipids are transported essentially completely in the form of a series of lipoproteins. The lipoproteins of blood represent not a single or a few specie (s), but rather a whole range of molecular entities from sizes approximating that of gamma globulin to tremendous sizes, such as those familiar from dark field microscopy as the chylomicrons. A compound such as cholesterol finds itself as a constituent of every single class of lipoproteins that has been analyzed. Therefore, we have immediately before us the possibility, if the various lipoproteins differ in concentration from person to person, which they do,

Chapter III

THE BLOOD LIPID FACTOR IN CORONARY HEART DISEASE

A PREREQUISITE *to evaluation of the blood lipid factor in* coronary heart disease is a concept of our present-day knowledge of the nature of the circulating blood lipids Two major modalities *of characterization have been applied to the blood lipids, the* first being chemical and the second being largely physical in nature Historically the chemical characterization preceded the physical *characterization, primarily the result of the earlier avail*ability of chemical techniques for analyses There can, of course, exist no *real* conflict between such modalities of analysis nor can there be any inconsistency in the results derived therefrom, providing both types of analyses are correct There exist, however, many good reasons to consider that the more modern physical *techniques for analysis of the blood lipids may be of the greater* value For the physical techniques describe the blood lipids in a state resembling closely that in which they exist in the blood. *Second, they provide a more intimate characterization* and delineation of the various blood lipids of potential interest in the problem of coronary heart disease The detailed basis for these *statements will become apparent in later discussions*

Chemically, the lipids of the blood are comprised largely by cholesterol, some of it free and some of it esterified with various fatty *acids, triglyceride or neutral fat,* phospholipids, free fatty acids, and possibly by several other constituents at very low abundance. The first three are certainly the major constituents *on the basis* of abundance The results of modern physicochemical techniques applied to the problem of the blood lipids show clearly that the chemical entities described above do not

rates even though very small molecules (such as glucose) do not. The second property of lipoproteins that makes them especially adaptable to ultracentrifugal analysis is the fact that they possess a physical density (grams/milliliter) that is considerably different from the density of the much more abundant *proteins* of blood. Whereas the density of the proteins of blood is approximately 1.3 grams per milliliter, the density of the most dense lipoproteins of blood is only 1.15 and the density of other lipoproteins range downward from this value to values even below 1 gram per milliliter. This means that if a solution is prepared from serum by the addition of sodium chloride or some other salt or sugar which thereby places the solution density between the density of the lipoproteins and that of the proteins, it is possible to effect a neat separation of the proteins and lipoproteins. The lipoproteins then *float* in the ultracentrifuge while the proteins *sediment*. This is the first step in lipoprotein analysis of serum. Once the lipoproteins have been separated from the proteins by this method, they are available for the step known as the analytical step which utilizes a larger ultracentrifuge equipped with an optical system for determining the kinds of lipoproteins that are present and the concentrations of each type present in a serum sample. It is customary in ultracentrifuge practise to refer to the speed to which any particle migrates under the effect of an intense gravitational field as its sedimentation rate, or migration rate, in "S units." The "S" stands for Svedberg and is so named in honor of The Svedberg who invented and pioneered the *ultracentrifuge*. Thus, if one were speaking about serum albumin molecules, which migrate in an ultracentrifuge under standardized conditions with 4 arbitrary units of speed, the albumin molecules would be referred to as molecules of the 4S, or 4 Svedberg, class. The *proteins*, which are more dense in general than the solutions in which they are migrating, sediment outward in the centrifugal field, or in the direction of the centrifugal field. The units of migration are chosen to be positive in this direction, so albumin would have a migration rate of *plus* 4 units of speed in Svedberg units. However, under the usual circumstances of lipoprotein analysis, the lipoproteins are made to undergo flotation *toward* the center of rotation, rather than

that a specified amount of cholesterol in the blood can mean very different things from one person to another. The same considerations would apply to phospholipids or to triglyceride, a specified amount of *either of these substances meaning possibly* very different things in different people. This can be restated that a specified chemical constituent (such as cholesterol) in one person may be primarily in one type or in a few types of lipoprotein, whereas in another person that same chemical compound might be distributed *primarily in other types of lipoprotein.* The intimate characterization of the lipoproteins in the blood and their measurement is at present most effectively and easily achieved by the physical technique of ultracentrifugation There is no other method which provides the detail concerning the distribution of types of lipoproteins in the blood and the measurement of the various classes that is even remotely comparable with the quality of data obtainable via the ultracentrifugal technique. That this technique will in the future be the best way of analyzing the lipoprotein distributions in blood is of course not foreseeable Should any simpler, more effective, or more critical technique be evolved, it would certainly be of great value to utilize such a newer technique for the analysis of the blood lipoproteins, although at present no such technique is in the offing. One might ask whether other techniques are available which for practical clinical purposes might serve adequately, even though for research purposes the ultracentrifugal technique is a necessity. The answer is that some of the highly practical *clinical* questions (which will be dealt with later in this book) require the ultracentrifugal analysis of the distribution of serum lipoproteins for most effective identification of the type of disorder involved and for the handling of those disorders in a medical management sense There are two properties of the lipoproteins of human blood which make the ultracentrifuge especially useful in their analysis The first property of the lipoproteins is their very large size The ultracentrifuge is an instrument which is in principle the same as an ordinary centrifuge, and hence particle size is of major consequence. With the powerful centrifugal fields available in the ultracentrifuge the lipoproteins in the blood are of large enough size to migrate at reasonable

flotation rate in S_f units, and that their concentrations can be measured in the usual clinical terms of milligrams per hundred milliliters directly from the ultracentrifugal analyses. There is one caution, however, that is important to stress. In the earliest centrifuge work lipoproteins were studied in a relatively dilute solution and their values were reported *directly* in terms of migration rates in S_f units. However, for certain purposes of precision and accuracy it became convenient to study the lipoproteins ultracentrifugally in more concentrated solutions. Under these conditions lipoproteins tend to slow themselves down in migration rate because of their being in high concentration. As a consequence all migration rates must be corrected in a standard manner before reporting of results. This correction can be very precisely applied and should be applied. There is no question of error involved in the use of concentrated solutions provided the appropriate corrections are applied. When this correction is applied, the lipoproteins are reported in terms of *Standard* S_f units, or "S_f^0 units." The word, standard, or the superscript, zero, applied to S_f means that the worker has applied all the corrections necessary for proper analysis of ultracentrifuge diagrams. Certain workers in the field have not fully appreciated the significance of the necessity to report ultracentrifuge results in the standard flotation rate, or S_f^0 units and have used concentrated solutions for ultracentrifugal analyses without applying the corrections. They have reported their work directly in S_f units. Such work is neither comparable to the early work in dilute solution[13] nor is it comparable to the correct method of ultracentrifugal analysis, employing standard S_f units. Therefore the reader is urgently cautioned to view with skepticism any report of ultracentrifugal analyses of lipoproteins in disease states or in health, where concentrated solutions have been utilized and where the results are reported in uncorrected S_f units instead of the standard S_f units in which they should be reported. A case in point where erroneous clinical conclusions were reached because of failure to utilize standard flotation rates is in the work of certain laboratories reported in the so-called Cooperative Study of Lipoproteins and Atherosclerosis[14].

The lipoproteins of human blood are divided into two broad major groups, the group of largest abundance and of primary

outward in the direction of the centrifugal force. In other words since the lipoproteins are migrating in a solution more dense than themselves, they migrate inward against the direction of centrifugal field. In order to avoid the cumbersome use of negative units for such flotation, a unit was introduced some ten years ago known as the *Svedberg of flotation*, or "S_f unit"[11]. This means precisely the same in terms of units of speed as for the proteins, except that materials are floating instead of sedimenting. Thus, if a lipoprotein floats as fast as albumin sediments the lipoprotein is called a molecule of the $4S_f$ class to correspond to the nomenclature of 4S for the albumin molecule. The description of lipoproteins in terms of flotation rate in S_f units is more than just a physical measurement, since it proves convenient as an actual naming system for the various lipoproteins. Had it turned out that nature were extremely simple and there were only a few lipoprotein species present in human blood, they might have been named by such terms lipoprotein one, two, and three, or lipoprotein A, B, and C. However, the studies of human blood have *shown that there exists an entire host of lipoproteins ranging in* size from the smallest, which are approximately 200,000 in molecular weight, up to the largest which are millions of millions in molecular weight, with a great number of intermediary species *being known to exist. There just wouldn't be enough letters in* the alphabet to name them by arbitrary names Furthermore naming of the lipoproteins by the physical measurement of the number of Svedbergs of flotation of migration rate proves to be very useful, for the name means something in terms of a physical constant that can be reproduced under standard conditions by workers anywhere in the world with ultracentrifugal equipment. In all the subsequent discussions of the relationships of lipoproteins with coronary heart disease, lipoproteins will be named in terms of their migration rate in the ultracentrifuge under a set of arbitrarily defined standard conditions in S_f units The precise technical details of ultracentrifugation have been described in extenso elsewhere[12]. It is neither the purpose of this discussion nor this book to present such technical issues in detail For our present purposes it is sufficient to note that a large number of lipoproteins exist in human serum, that they are named by their

teins between any two of these dividing points The sum of concentrations of all the lipoproteins between flotation rates of s_f0 and s_f12 is referred to as the concentration of the s_f0-12 lipoprotein class. Correspondingly the sum of concentration of all the lipoproteins floating between the rates of s_f12 and s_f20 is referred to as the concentration of the s_f12-20 lipoprotein class. Similar procedures are used to determine the s_f20-100 and s_f100-400 lipoprotein classes. Most lipoprotein analyses are reported in these general bands. The question may be raised as to whether there might not be some better banding or some sub-banding that would be of importance. Such a possibility can never be ruled out, but it can be stated that, if in the future a different banding should be proved to be of greater value, an old ultracentrifugal run can be re-evaluated in terms of such new banding. At the moment there appears to be little advantage with respect to the study of a disease such as coronary heart disease of any banding beyond that which has already been described. Indeed for certain purposes the three classes, s_f12-20, s_f20-100 and s_f100-400 lipoproteins are added together and reported as the s_f12-400 lipoprotein class. This type of procedure is one of general applicability. Thus, if the concentrations of s_f20-100 and s_f100-400 lipoproteins are added, the sum of these two concentrations can be referred to as the concentration of the s_f20-400 lipoprotein class.

It is now possible to turn attention to the problem of whether or not any of the lipoproteins of human blood are associated in some way with coronary heart disease. The ultimate objective sought might be restated here, namely, a measurement which would be related in a *predictive* sense to the rate of development, or of the degree of development of sub-clinical coronary heart disease. If human blood lipoproteins are found to be associated with coronary heart disease, the first question that must be asked is, "*Which* lipoproteins are involved, the s_f0-12 class, the s_f12-20 class the s_f20-100 class, or the s_f100-400 class, or some combination of these classes?" The next question to be answered is, "If all classes or several classes of lipoproteins are involved, does the measurement of each class provide *independent* information?" It is of course possible that one class of lipoproteins may be simply a "rider," being abnormal simply because the level of this class of

interest with respect to coronary heart disease being that known as the low density lipoproteins. Such lipoproteins are all characterized by densities of 1.05 gms/milliliter or less. There are, in addition, three groups of lipoproteins which are referred to as high-density lipoproteins, all of densities 1.05 gms/milliliter or greater. The high-density lipoproteins will be referred to in a subsequent chapter under the subject of various chemical analyses in connection with prediction tests for coronary disease (Chapter XV) and will not be dealt with further at this point. The low-density lipoproteins under standard conditions, or in Standard S_f units, migrate with rates of 0 units up to some 40,000 units of speed. In the vast majority of human cases the bulk of these lipoproteins are contained within the range of speeds from 0 to 400 units. This band is also incidentally the most readily studied by ultracentrifugal procedures. Even within the region of s_f0 to s_f400 there exists a very large number of lipoprotein species. One cannot be sure, at this time, of the exact number of species that is present. If measurements were to be made of lipoproteins in relationship to coronary heart disease, the analysis of concentration of each and every lipoprotein class from s_f0 to s_f100 would be an almost insurmountable task However, there are alternatives to measurement of each and every lipoprotein within this region from s_f0 to s_f100, alternatives which have been shown to be highly productive. One such alternative is to divide the region from s_f0 to s_f400 into several bands. The actual choice of limits of bands is somewhat arbitrary, although there appear to be some regions of logical sub-division Such regions were chosen through large experience with ultracentrifugal analyses, which revealed that *points such as s_f12, s_f20 and s_f100 are what might be called natural* dividing points Many humans show a minimum in their lipoprotein concentrations in these particular regions. As a result of using such dividing points, lipoproteins are characterized as those which float between the rates of s_f0 and s_f12, those which float between the rate of s_f12 and s_f20, those which float between the range of s_f20 and s_f100, and those which float with rates between s_f100 and s_f400 A convenient, practical procedure that has been utilized in over 100,000 routine ultracentrifuge analyses of human blood is to measure the sum of the concentrations of all lipopro-

ing such investigations. In such a study one is desirous of minimizing any disturbing factors extraneous to the factor of the existence of clinical coronary heart disease itself. Thus to contrast the serum lipoprotein levels in patients with clinically established coronary heart disease with persons in overt health (those without clinical manifestations of coronary heart disease), one would not like to have the patients with clinical coronary heart disease in a metabolic state unusual for them. For example, one would prefer to have patients who are on the same diet which has characterized them during the period of life before their clinical manifestation of heart disease. The possibility had existed and has now been abundantly confirmed that dietary change can of itself profoundly alter serum lipoprotein levels One would prefer that the patients be at precisely the same weight that had habitually characterized them before their episode of clinical coronary heart disease. One would prefer that they be taking no medications that they were not taking before their episode of clinical coronary heart disease Quite obviously the various clinical sources of material available for this type of study do not allow for attainment of such ideal clinical cases. For many, many years numerous physicians have had definite ideas concerning diet, weight control, and certain medications in relation to coronary heart disease, wholly apart from blood lipid considerations. Hence, patients who present with clinical coronary heart disease have necessarily received some advice and management which may alter their metabolic status. Nevertheless one can exclude cases where more than a certain amount of weight has been lost since the clinical episode, and if such exclusions are made before the lipoprotein analyses are available, there is very little possibility of biassing the material in this way. Furthermore, in the very acute phase of an episode such as myocardial infarction there is the possibility of shock and its attendant metabolic alterations which one would also want to avoid. For this reason the study of patients with clinically established coronary heart disease has been limited to those who were at least six weeks beyond the occurrence of an acute episode of myocardial infarction The acute phase has been studied in addition, but this was not part of the original program of evaluation The question of matched con-

lipoproteins may be highly correlated with the level of some other lipoprotein class that is directly involved in coronary heart disease A third major question that would arise is, "At what stage in the evolution of coronary heart disease does any association between lipoproteins and the disease first manifest itself?" In the general discussion of possible factors associated with coronary heart disease it was pointed out that if a variable becomes abnormal *after* the clinical event is manifest, but is not abnormal or unusual during the sub-clinical stage, it would not be of especial interest for the purposes desired. Therefore it is urgent to know how early in the evolution of the sub-clinical phase of coronary heart disease any disturbance of lipoprotein levels does manifest itself

For reasons of convenience and availability of material the earliest studies made concerning the possible association of lipoproteins with coronary heart disease were made on patients with established clinical coronary heart disease. The objections to the use of such clinical material as a final group were reviewed in detail in Chapter II, where it was demonstrated however that such material is an excellent starting point in this problem. As was also pointed out earlier, the alternative to the use of such material is to study a very large number of apparently healthy people and then to watch the evolution of coronary heart disease in this group. Such studies would allow not only for proof of association of lipoproteins with sub-clinical coronary heart disease but also a determination of how early in the sub-clinical phase of the disease any abnormality of lipoproteins is present. Both types of studies have by now been completed with highly conclusive results and the results of both types of studies will be presented below

THE STUDY OF LIPOPROTEINS IN PATIENTS WITH CLINICALLY MANIFEST CORONARY HEART DISEASE

While the study of patients with clinically established coronary heart disease leaves undetermined the issue of whether the clinical event might have possibly caused any abnormality discovered in serum lipoproteins, the great availability of clinical material *without a long delay period* such as a prospective followup study entails made this the procedure of choice for start-

nent is that the control subjects be closely comparable to the clinically diseased subjects except for the one fact that the control subjects do not show clinically-manifest coronary heart disease. It is of no moment whatever to obtain a group of subjects as controls who are free of any possible tinge of sub-clinical coronary heart disease

Studies have been made of all the four major low-density lipoprotein classes, s_f0-12, s_f12-20, s_f20-100, and s_f100-400 in several age categories of males with and without clinical coronary heart disease in the form of documented myocardial infarction and in several age categories of females with and without clinical coronary heart disease The mean values for each of these lipoprotein classes in the subjects with clinical coronary heart disease and their matched controls are presented in Table I. It is evident from statistical analyses of these data for the sub-segments of the entire series of patients where there are adequate numbers of cases or for the entire series of cases and their age-and sex-matched controls, that the following is true:

(1) The s_f0-12 lipoproteins are significantly and appreciably higher in the clinical coronary heart disease cases than in their matched controls.

(2) The s_f12-20 lipoproteins are significantly and appreciably higher in the coronary disease cases than in their matched controls

(3) The s_f20-100 lipoproteins are significantly and appreciably higher in the coronary disease cases than in their matched controls

(4) The s_f100-400 lipoproteins are significantly and appreciably higher in the coronary disease cases than in their matched controls

The first large step forward can be taken, namely, to make the statement that the low-density serum lipoproteins are distinctly different, on the average, in patients with clinical coronary heart disease from those in their matched controls. It can be stated further that elevated levels of several serum lipoprotein classes are in some way associated with clinical coronary heart disease. Next must come the issue of whether *independent* information is provided by the measurement of *each* of these four lipoprotein classes.

trol subjects arises. Certain aspects of the choice of control subjects should be obvious, among these are such aspects as matching the cases of clinical coronary heart disease by sex, age, *and by general source of origin of the subjects. Since ideally* the study to be described subsequently is the one of choice, namely, where the coronary disease group arises de novo out of a previously studied large population sample, it is desirable in this study which compares persons with and without overt clinical coronary heart disease that as nearly as possible the control subjects be representative of the population segment out of which the clinical coronary disease cases had arisen. For example, it would be extremely poor matching if one were to use indigent patients with coronary heart disease as the disease subjects and a well-to-do population sample as the control subjects, or vice versa. This is not an academic matter at all, since the problem of selection of sources of clinical material is a very serious one often inadequately appreciated by clinical investigators.

One source of confusion has especially plagued the minds of many who have considered the evidence relating blood lipid findings with coronary heart disease. This is the question of whether or not the control subjects are free of coronary atherosclerosis First of all, it should be stated that this entire question *of the difference in blood lipids between subjects with clinical* coronary heart disease and control subjects is being developed wholly without any reference to atherosclerosis. Hence, there is simply no need whatever to ask the question of whether or not the control subjects are free of coronary atherosclerosis Second, even if we were to ask the question of whether there does exist sub-clinically some degree of coronary heart disease going on in those who have not yet manifested clinical symptoms, the fact that the answer is, yes, is wholly immaterial to the issues at hand. At this point, we are simply asking the question, "Is there a difference in lipoprotein levels of the various lipoprotein classes between those individuals who have demonstrated documented clinical coronary heart disease and those who have *not* demonstrated clinical coronary heart disease?" There is no inference, *intent to infer, or effort to prove that subjects chosen as controls* are free of sub-clinical coronary heart disease. All that is perti-

In essence the question to decide is whether s_f12-20 lipoproteins are *intrinsically* elevated in clinical coronary heart disease or whether they are elevated simply as a reflection of the elevation in s_f0-12 lipoproteins which characterizes clinical coronary heart disease. Perhaps another way to express this concept more clearly would be to ask the question, "If *all other things* were equal concerning the cases of clinical coronary heart disease and the matched controls, would the s_f0-12 lipoproteins still be elevated in the coronary disease cases?" Similar questions could be asked for the observed elevation in level of the s_f12-20 lipoproteins, the s_f20-100 lipoproteins, and the s_f100-400 lipoproteins, respectively. This approach can be made more simply if at first the total group of lipoproteins from s_f0 to s_f400 is subdivided into two major classes, s_f0-12 and s_f12-400 bands instead of into four groups. Then if the cases of documented myocardial infarction are matched with random control cases *at the same* s_f0-12 lipoprotein levels, is it true that the s_f12-400 lipoproteins are *still* elevated in the coronary disease cases relative to those in the matched controls? The direct tests of this issue are presented in Table II. The results there provide excellent evidence that the cases of myocardial infarction, matched with the control cases upon s_f0-12 lipoprotein level, do

TABLE II

DEMONSTRATION OF THE INDEPENDENT ELEVATION OF S_f12-400 LIPOPROTEIN LEVELS IN MYOCARDIAL INFARCTION CASES IN COMPARISON WITH MATCHED CONTROLS

(Myocardial infarction cases matched with random controls upon age, sex, and upon S_f0-12 lipoprotein levels)

Group	*Number of Cases*	*S_f0-12 Lipoprotein Level (mg/100ml)*	*S_f12-400 Lipoprotein Level (mg/100ml)*
40-49 year old male Myocardial Infarction Survivors	113	420.4	321.6
40-49 year old Matched Controls	113	422.2*	255.4
	Difference	(Myocardial Infarctions − Controls)	+ 66.2 (p << 0.001)

*The slight diff…
controls indi…

TABLE I

SERUM LIPOPROTEIN LEVELS IN PERSONS WITH AND WITHOUT OVERT CLINICAL CORONARY HEART DISEASE

(*Myocardial Infarction as Criterion**)

MALES	*Mean Age* (*years*)	*Number of Cases*	*Mean* S_f*0-12 Level* (*mg/100ml*)	*Mean* S_f*12-20 Level* (*mg/100ml*)	*Mean* S_f*20-100 Level* (*mg/100ml*)	*Mean* S_f*100-400 Level* (*mg/100ml*)
30-39 year age group						
Myocardial Infarction	31.8	11	485.0	101.3	152.1	72.3
Matched Controls	34.8	834	356.2	51.5	92.5	52.0
40-49 year age group						
Myocardial Infarction	44.5	113	420.4	88.7	134.3	98.7
Matched Controls	44.5	399	382.9	57.0	108.5	67.2
50-59 year age group						
Myocardial Infarction	54.0	210	413.4	83.3	124.3	77.3
Matched Controls	54.0	153	385.3	56.2	106.0	60.0
60-69 year age group						
Myocardial Infarction	63.9	144	407.7	82.2	121.2	61.7
Matched Controls	63.9	35	365.5	52.5	82.0	43.5
FEMALES						
35-69 year age group						
Myocardial Infarction	57.2	59	426.8	110.8	116.4	99.2
Matched Controls	57.2	110	367.0	54.5	87.8	26.0

*All myocardial infarction cases represent survivors, eight weeks or more beyond the acute episode.

In essence the question to decide is whether s_f12-20 lipoproteins are intrinsically elevated in clinical coronary heart disease or whether they are elevated simply as a reflection of the elevation in s_f0-12 lipoproteins which characterizes clinical coronary heart disease. Perhaps another way to express this concept more clearly would be to ask the question, "If *all other things* were equal concerning the cases of clinical coronary heart disease and the matched controls, would the s_f0-12 lipoproteins still be elevated in the coronary disease cases?" Similar questions could be asked for the observed elevation in level of the s_f12-20 lipoproteins, the s_f20-100 lipoproteins, and the s_f100-400 lipoproteins, respectively. This approach can be made more simply if at first the total group of lipoproteins from s_f0 to s_f100 is subdivided into two major classes, s_f0-12 and s_f12-400 bands instead of into four groups. Then if the cases of documented myocardial infarction are matched with random control cases *at the same* s_f0-12 lipoprotein levels, is it true that the s_f12-400 lipoproteins are *still* elevated in the coronary disease cases relative to those in the matched controls? The direct tests of this issue are presented in Table II. The results there provide excellent evidence that the cases of myocardial infarction, matched with the control cases upon s_f0-12 lipoprotein level, do

TABLE II

DEMONSTRATION OF THE INDEPENDENT ELEVATION OF S_f12-400 LIPOPROTEIN LEVELS IN MYOCARDIAL INFARCTION CASES IN COMPARISON WITH MATCHED CONTROLS

(Myocardial infarction cases matched with random controls upon age, sex, and upon S_f0-12 lipoprotein levels)

Group	*Number of Cases*	*S_f0-12 Lipoprotein Level (mg/100ml)*	*S_f12-400 Lipoprotein Level (mg/100ml)*
40-49 year old male Myocardial Infarction Survivors	113	420.4	321.6
40-49 year old Matched Controls	113	422.2*	255.4
	Difference (Myocardial Infarctions-Controls)		+ 66.2 ($p << 0.001$)

*The slight d[illegible] controls in[illegible]

show a higher mean s_f12-400 lipoprotein level than do the controls. Therefore, evidence is at hand of the independent association between coronary heart disease and the s_f12-400 lipoprotein levels. Stated otherwise, while we get evidence from the measurement of s_f0-12 lipoprotein levels concerning coronary heart disease, we derive *additional* and truly independent information from the measurement of the s_f12-400 lipoprotein levels.

Similarly, the problem can be approached the other way around. If the documented cases of myocardial infarction are matched with random control cases at the same s_f12-400 lipoprotein level, is it true that the s_f0-12 lipoprotein levels are still elevated in the coronary disease cases as compared with the matched controls? A direct test of this point was made, the results of which are presented in Table III. Those results indicate clearly that even when the myocardial infarction cases are matched with the control cases at the same values of the s_f12-400 lipoproteins, the myocardial infarction cases still show a significantly and appreciably higher level of s_f0-12 lipoproteins than do the matched controls. Therefore, this provides direct evidence for the independent association of the s_f0-12 lipoproteins with coronary heart disease. Thus, while we get evidence from the measurement of the s_f12-400 lipoprotein levels concerning coronary heart disease,

TABLE III

DEMONSTRATION OF THE INDEPENDENT ELEVATION OF S_f0-12 LIPOPROTEIN LEVELS IN MYOCARDIAL INFARCTION CASES IN COMPARISON WITH MATCHED CONTROLS

(Myocardial infarction cases matched with random controls upon age, sex, and upon S_f12-400 lipoprotein levels)

Group	*Number of Cases*	*S_f12-400 Lipoprotein Level (mg/100ml)*	*S_f0-12 Lipoprotein Level (mg/100ml)*
40-49 year old male Myocardial Infarction Survivors	113	321.7	420.4
40-49 year old Matched Controls	113	322.8*	381.9
Difference (Myocardial Infarctions Controls)			+ 38.5 ($p << 0.001$)

*The slight difference in S_f12-400 lipoprotein level between the infarction cases and the controls indicates how well the two groups were matched upon this variable.

we derive additional and independent information from the measurement of the S_f 0-12 lipoprotein levels

Looking ahead to some of the applications of these findings, it becomes apparent why such information is crucial. If two independent groups of lipoproteins determine a person's status with respect to coronary heart disease, it is clear that the measurement of only *one* of these groups cannot possibly provide a complete picture of that person's status. A person might, for example, be quite satisfactory in terms of his level of S_f 0-12 lipoproteins and hence his outlook with respect to coronary disease be considered good on this basis, but on the other hand with an enormously elevated level of S_f 12-400 lipoproteins the outlook would be changed to a poor one in spite of the favorable level of the S_f 0-12 lipoproteins.

In an entirely analogous manner each of the subcomponents of the S_f 12-400 group of lipoproteins, namely the S_f 12-20, S_f 20-100, and S_f 100-400 lipoproteins can be tested for independent association with clinical coronary heart disease. This has been done successively for each of these lipoprotein classes[15]. It can be stated that S_f 12-20 lipoproteins, S_f 20-100 lipoproteins, and S_f 100-400 lipoproteins, respectively, are all *independently* associated with clinical coronary heart disease

In summary, the study of established clinical coronary heart disease (utilizing documented myocardial infarction cases) is that low-density lipoproteins of the blood, at least of these four classes, the S_f 0-12, 12-20, 20-100, and a *100-400* classes, are significantly elevated in clinical coronary heart disease and that each class of lipoproteins provides information independent of that provided by all the others. *Therefore* the best [illegible]

[illegible] that there exist certain potential pitfalls in the application, for predictive purposes in the subclinical phase of coronary heart *disease*, of information derived from the study of after-the-fact cases of clinical coronary heart disease. Among such potential pitfalls is the possibility that a clinical episode of coronary *heart disease* itself is the cause of the lipoprotein elevation. The only way to evaluate this possibility

is to show whether the association between lipoprotein levels and coronary heart disease holds *during the sub-clinical phase,* well in advance of the clinical episode. This involves the study of lipoprotein levels in a reasonable sample of the population-at-large with follow-up observation for the development of de novo clinical coronary heart disease.

THE PROSPECTIVE STUDY OF THE RELATIONSHIP BETWEEN SERUM LIPOPROTEINS AND CORONARY HEART DISEASE IN ITS SUB-CLINICAL STATE

The major potential value of what association exists between lipoproteins and coronary heart disease lies in the extent of such association during the sub-clinical phase. Any association demonstrated for the sub-clinical phase provides immediately information of potential value in the advance prediction of clinical coronary heart disease and of potential value in the guidance of a program for prevention of clinical coronary heart disease It was recognized early in the study of this problem that development of the information concerning the nature of the association of the sub-clinical coronary heart disease with serum lipoproteins was absolutely essential The establishment of the relationship of the serum lipoproteins with *clinical* coronary heart disease was an early step, possible because of the ready availability of material Those studies did provide a great deal of information of use while the results of the prospective study in the sub-clinical phase were awaited. The essence of a study designed to determine whether the association that has been proven between serum lipoproteins and clinical coronary heart disease also holds in the sub-clinical phase centers about follow-up observations A large population sample of individuals in overt health, that is, free of any evidence of clinical coronary heart disease, is studied with respect to lipoprotein levels Then, for a period of one or more years such individuals are observed without any effort being made to alter their lipoprotein levels and, indeed, without them being aware of the findings of the lipoprotein analysis. If the sample of the population studied is sufficiently large, then over a period of one to three years there is expected a reason-

able incidence of development of manifestations of clinical coronary heart disease in the form for example of angina pectoris, myocardial infarction, or death due to coronary heart disease. Since angina pectoris is a subjective diagnosis, this is the least safe to use as a clinical manifestation of the development of coronary heart disease. Hence in the considerations of an association between the sub-clinical phase of coronary disease and lipoproteins, the development of angina pectoris was not used as a primary criterion However, documented myocardial infarction, coronary thrombosis with death, and sudden death due to coronary heart disease were used as acceptable events of a clinical type to identify those individuals who passed from the sub-clinical phase of coronary heart disease to the clinical phase. If the lipoprotein association with coronary heart disease which was proven above with respect to the clinical phase also holds in the sub-clinical phase, it would be expected that the mean level of the various classes of lipoproteins in those individuals in the population sample who develop clinical coronary heart disease will be the same as the mean level found in the cases of established clinical coronary heart disease This would be so unless the clinical coronary heart disease has of itself altered the lipoprotein levels or that some factor attendant upon clinical coronary heart disease such as alteration in diet or medication has altered the lipoprotein levels If the lipoprotein elevation is an abnormality present before the clinical event and is unaltered by the clinical event itself, then it would be expected that the lipoprotein level determined in a group of people before they have a myocardial infarction should be the same as in such groups of people studied after the infarction

The requisite large scale follow-up study has now been completed[16, 17] Several sources of men in clinical health were utilized to provide lipoprotein samples before the follow-up observation period These sources included:

(1) Persons involved in the Framingham United States Public Health Service Heart Project.

(2) Employees of the Eastman Kodak Corporation.

(3) Employees of United Air Lines

(4) Employees of the Los Angeles Civil Service Commission.

(5) Employees of Pan American Airlines.

(6) Employees of the University of California Radiation Laboratory.

In all there were 4,088 subjects under study. During a one to three year follow-up period, the period being variable for the various sources, there occurred 26 cases of documented myocardial infarction, coronary thrombosis, or coronary heart disease with death in individuals who had been previously classified at the time of entry into the study as being in clinical health. Since being in clinical health means only that overt manifestations of coronary heart disease are absent, *this is of course tantamount to* saying that such individuals were *in various stages of the development of sub-clinical coronary heart disease,* since this is the real meaning of sub-clinical coronary heart disease. In Table IV are listed the cases of proven documented clinical coronary heart disease which have evolved out of the population sample under follow-up together with their lipoprotein values for the various classes. Also in Table IV are given the mean values for the matched population sample itself out of which the cases have arisen, matched by age with the cases of documented de novo coronary heart disease (according to the above-listed criteria). These data show clearly that the persons who later develop clinical coronary heart disease are those who were previously shown to have elevated lipoproteins of the four low-density lipoprotein classes, $S_f0\text{-}12$, $S_f12\text{-}20$, $S_f20\text{-}100$, and $S_f100\text{-}400$. Furthermore, the extent of lipoprotein elevation that had characterized the de novo cases one to three years before is closely similar to that found previously *for established cases of coronary heart disease* described above These data establish conclusively that the lipoprotein associations previously proven for clinical coronary heart disease *also hold for the sub-clinical phase, at least* one to three years before the clinical phase. This of course implies that lipoprotein measurement *must* have predictive value in selecting out the likely candidates for the future development of clinical coronary heart disease. The exact manner in which such data are used for such predictive purposes will be treated in Chapter V.

However, at the present time it is important to point out that the data derived from the prospective follow-up study show clearly that none of the concepts concerning lipoproteins and coronary heart disease derived from the study of the established clinical entity were in any way incorrect or misleading. Indeed the agreement between the study of established coronary heart disease and de novo coronary heart disease could hardly have been better.

There had previously existed much indirect evidence which would have suggested that the abnormality in blood lipids,

TABLE IV (a)

LIPOPROTEIN LEVELS IN 26 MEN (DETERMINED WHILE THEY WERE CLINICALLY HEALTHY) WHO SUBSEQUENTLY DEVELOPED DOCUMENTED CLINICAL CORONARY HEART DISEASE

(1 to 3 year follow up period)

Case	Age at Study	S_f 0-12 (mg/100ml)	S_f 12-20 (mg/100ml)	S_f 20-100 (mg/100ml)	S_f 100-400 (mg/100ml)
1	34	576	85	155	139
2	35	719	139	271	134
3	37	309	58	228	130
4	40	418	72	110	121
5	40	452	63	251	184
6	40	388	52	74	16
7	40	473	90	179	237
8	42	206	81	217	118
9	42	345	76	110	56
10	44	461	92	99	47
11	45	403	112	101	137
12	46	520	128	175	43
13	47	410	65	134	119
14	49	329	72	92	52
15	49	414	81	164	38
16	49	318	58	123	67
17	49	403	81	166	85
18	51	580	65	139	16
19	51	497	110	125	110
20	51	605	116	179	72
21	51	403	67	128	36
22	52	482	56	103	52
23	56	318	119	96	43
24	57	381	78	108	67
25	57	524	130	136	26
26	58	535	134	190	94

expressed in the form of an elevation of certain serum lipoproteins, *would* characterize individuals *in advance* of the development of clinical coronary heart disease. Such evidence derived from the abnormalities in lipids in diabetes mellitus (pre-insulin period at least), in nephrosis, and in myxedema, and in a variety of familial entities—all of which are characterized by premature coronary heart disease. In all of these cases the lipid abnormality it known to precede the development of vascular disease. However these were all special situations, and while they provided highly suggestive leads, it was essential, in dealing with the problem of coronary heart disease in the vast bulk of the population, to prove directly, as it has now been done conclusively, that the blood lipid abnormality does indeed precede the clinical development of coronary heart disease. The ability to make predictions concerning the rate of development and severity of sub-clinical coronary heart disease one to three years in advance of its conversion to clinically-manifest disease is of course a major step forward. Next it is important to ask the question, "Is such predictability limited to one to three years before the development of overt, clinical coronary heart disease?" The evidence just presented does not *limit* the predictability of future coronary disease from lipoprotein measurement to three years

TABLE IV (b)

COMPARISON OF MEAN LIPOPROTEIN LEVELS FOR 26 DE NOVO CLINICAL CORONARY DISEASE CASES WITH THOSE FOR THE AGE MATCHED POPULATION SAMPLE FROM WHICH THEY AROSE (MEN)

	Mean Age (years)	*Mean S_f 0-12 (mg/100ml)*	*Mean S_f 12-20 (mg/100ml)*	*Mean S_f 20-100 mg/100ml)*	*Mean S_f 100-400 mg/100ml)*
De Novo Documented Clinical Coronary Disease Group	46.6	442.2	87.7	148.3	87.3
Age-Matched Healthy Population Sample out of which the coronary disease cases arose	46.6	386.0	57.6	110.3	68.0
Difference (De Novo Coronary Cases—Healthy Population Sample)		+ 56.2	+ 30.1	+ 38.0	+ 19.3
		$p << 0.01$	$p << 0.001$	$p < 0.01$	$p \sim 0.05$

Rather, what is meant is that such evidence by and of itself only allows assurance of the predictability for one to three years, since this was the time period of the follow-up study. However it is possible through incorporation of other findings referable to lipoprotein levels in individuals to demonstrate that the abnormality in serum lipoproteins is undoubtedly present a much longer period than three years before the development of clinical coronary heart disease All the evidence available suggests that the lipoprotein abnormality may be used to pre-select individuals who are likely to develop clinical coronary heart disease as many as ten or twenty years before the development of the overt clinical entity

In order to determine directly the maximum period before the development of clinical coronary heart disease that the lipoproteins may be used in prediction of risk of future clinical coronary heart disease, it would be necessary that the follow-up studies described above be carried on for five, ten, fifteen, twenty or twenty-five years These follow-up studies will of course be carried on as an extension of those that have already been done. However, it is not necessary to await the results of the five, ten, fifteen, or twenty year follow-up periods to determine the answer of duration of predictive value, since *it is* possible to attain this answer now The basic question underlying the problem of how long *beyond* three years the predictive value of lipoprotein measurement is valid is that of knowing whether people in the population tend to retain their relative positions *with respect to each other* in terms of lipoprotein values This point may be illustrated by considering two representative individuals in the population The data presented above would indicate that, if we study one individual with high lipoprotein levels and another individual with low lipoprotein levels, during the one to three year period following the lipoprotein measurement the person with high values is more likely to develop coronary heart disease than the one with low values. This is true because data accumulated already have shown that the average value and the distribution of values of the lipoproteins studied in advance are higher in those who go on to develop coronary disease than in those who do not Therefore if studies had demonstrated that

the person with high lipoprotein levels had remained high for five years, and the person with low levels had remained low for five years before this study was started, then the prediction would be valid for an additional five year period. This is evident, since it would have been possible to determine five years earlier that the same relative position characterized the two people under consideration. Similarly if instead of 5 years such consistency in *relative* position with respect to lipoprotein level had been maintained for ten or fifteen years before the study, then the predictive value would have held for this corresponding ten or fifteen year period. The only situation in which the prediction available from the lipoprotein levels would have not been valid would arise when two individuals alter their relative positions appreciably on the lipoprotein scale over the five, ten, or fifteen year period under consideration. Again, to settle this issue directly would require that the population of individuals be followed with serial blood sampling for a period of five, ten, or fifteen years of adult life. Since the technical development of lipoprotein measurement is now only ten years old, it has not been possible to follow large numbers of individuals this long. However, it has been possible to follow individuals at every age period in adult life for a shorter period of time. That is, it has been possible to study individuals at 20 years of age during a two to five year period to the age of 22 or 25 years, individuals at 25 years of age to the age of 27 or 30 years, individuals 30 years of age to the age of 32 or 35 years, individuals at 35 years of age to the age of 37 to 40 years, and so on up to the age of sixty years. It has been shown that for these various spans, 20 to 25, 25 to 30, 30 to 35, and so on up to 55 to 60, individuals tend very strongly to retain their relative ranking on the lipoprotein scale. Since this has been shown to be true for every five year period between 20 and 60 years, there appears to exist *no* period during adult life when individuals tend to shift around in relative positions on the lipoprotein scale. Therefore it can be stated that individuals tend to retain their relative lipoprotein ranking in the population very well. This means that the abnormality in lipoproteins which was directly proved to be predictive of coronary heart disease at least one to three years before the development

of clinical coronary heart disease can be estimated to exist, in general, at least for periods of the order of ten or twenty years of adult life. Candidates for future clinical coronary heart disease can therefore be identified some ten to twenty years before the disease becomes overt, which means that the opportunity for institution of preventive measures is excellent.

There is no inference in any of these statements that the lipoprotein levels in a particular individual remain absolutely constant throughout adult life There does exist some short-term fluctuation and some long term fluctuation in individuals. However, in general, such fluctuations in levels of the crucial low-density lipoproteins are small enough such that persons in the lowest 10 or 20% of the population distribution tend to remain there, in spite of fluctuation, whereas persons in the highest 10% of the population tend to remain there. This, rather than the minor fluctuations that do occur, is the important issue at hand. One qualification of these statements is necessary. It will be shown later (Chapter IX and X) that diet and body weight are related to lipoprotein levels Therefore if an individual should significantly alter his dietary pattern and his body weight, it would be expected that his relative ranking in lipoprotein levels would be altered But such dietary and weight alterations are readily determined and hence need never provide confusion concerning the person's status Similarly certain clinical entities such as nephrosis or myxedema are associated with gross alterations in lipoprotein levels Hence no surprise would be occasioned by the occurrence of a shift in relative ranking of an individual with respect to others if he should develop clinical nephrosis or myxedema

The demonstration that lipoprotein levels are elevated during the sub-clinical phase of coronary heart disease years in advance of overt clinical manifestation is beyond reasonable doubt This finding carries with it the direct implication and the information which make it possible to predict the risk of future overt clinical coronary heart disease in individuals through blood lipoprotein measurement. The manner of use of the lipoprotein data for this predictive purpose and the extent of prediction possible will be elaborated in detail in Chapter V.

Chapter IV

THE BLOOD PRESSURE FACTOR IN CORONARY HEART DISEASE

It is a source of amazement that at this late date there should exist so much confusion with respect to the issue of the nature of the relationship of habitual blood pressure levels with coronary heart disease, both sub-clinical and clinical. A review of the evidence in the literature concerning the blood pressure and coronary heart disease indicates clearly that the actual data pertaining to this subject are not at all confusing, but rather that the interpretation of such data has often been faulty and has led to the current divergence and haziness of "authoritative" views. The specific problems of concern here are twofold,

(a) The extent of difference, if any, in the habitual blood pressure in those persons developing sub-clinical coronary heart disease at an excessive rate in comparison with those developing the disease at a slow rate

(b) If the habitual blood pressure is significantly related to the rate of development of sub-clinical coronary heart disease, it must be determined whether information is thereby provided independent of the information provided by the blood lipoprotein measurements

It is obvious why these are crucial issues in coronary heart disease. For, if the blood pressure is significantly related to the development of sub-clinical coronary heart disease, and if the information is *independent* of the lipoprotein information, then an additional tool, or an additional factor, is available for evaluation of any person with respect to the risk of later clinical coronary heart disease.

The evidence concerning the blood pressure is derived from many sources and types of evidence. Some of these sources are

indirect but have provided valuable clues crucial for a critical evaluation of the role of habitual blood pressure levels in coronary heart disease. The problem at hand, with respect to coronary heart disease, can be stated in a frame of reference similar to that for the blood lipoproteins. If one were to rank a large group of individuals in overt health upon their habitual blood pressures, without any knowledge of other factors, would it be true that coronary heart disease occurs with a greater frequency in those with elevated blood pressures than in those without such elevation? However, before consideration of the relevant data, let us review much of the ancillary evidence which can be regarded as being in the form of clues and suggestions. First, there is a long-standing clinical impression that coronary heart disease and hypertensive cardiovascular disease are in some way related. So strong has been this impression that in the minds of some physicians the two phenomena, hypertension and coronary heart disease, have been regarded as facets of the same problem. The direct, critical evidence relating these two phenomena is not nearly so good as the clinical impression would indicate. Second, there exists a wide spectrum of experimental data which suggests that hypertension is related to the development of arteriosclerosis of the large and medium-sized arteries. While evidence concerning arteriosclerosis is to be considered as suggestive, it will not be made the basis of any definitive case for the findings with respect to hypertension. The clinical and pathological literature show frequent recording of observations that areas of the arterial tree subjected to excessive pressure are characterized by premature and excessive degrees of arteriosclerosis. One such item of evidence arises from the study of the region of the aorta before and after a coarctation. Many pathology texts comment on the high degree of sclerosis in the area before the coarctation (the high pressure side) versus the much lower degree of sclerosis in the area after the coarctation (the low pressure side)[18]. There also exists experimental evidence derived both from studies of the dog and of the rabbit which indicates that the blood pressure is an important factor in promoting the degree of arteriosclerosis in the arterial tree. Wakerlin[19], in some critical studies in dogs, performed the following experiment. On one

group of dogs he performed a Goldblatt operation with constriction of the renal artery to produce a hypertension in the dog, whereas on the second group he performed a sham operation without constriction of the renal artery. Both groups of dogs were then maintained on an atherogenic regimen including thiouracil (for suppression of thyroid function) and the cholesterol feeding. Steiner and Kendall[20] had previously shown that in dogs this combined regimen would produce elevation of the blood lipids and subsequent arteriosclerosis. Wakerlin found that the degree of arteriosclerosis in the major arterial vessels was much greater in the group of hypertensive dogs than in the group of sham-operated non-hypertensive dogs, even though the average extent of elevation of the blood lipids and lipoproteins was the same for the two groups of animals This represents a rather clear-cut demonstration that the elevated blood pressure was itself a major factor in promoting arteriosclerosis Similar results were obtained by Heptinstall and Porter[21] in the study of the experimental rabbit being fed cholesterol. In this case hypertension was produced by a clip on the renal artery. Again, it was shown by these workers that the degree of arteriosclerosis in the aorta was much more marked in the hypertensive rabbits than in the normotensive group, both groups having experienced comparable blood lipid elevations

Turning now to the direct clinical evidence with respect to the relationship of hypertension with the entity of coronary heart disease rather than with arteriosclerosis, one finds a vast mass of literature replete with apparently conflicting statements and opinions One statement commonly found in textbooks and in the literature is that hypertension in the female sex is a factor in coronary heart disease whereas it is not a factor in the male sex. Another variant of this same statement is that coronary heart disease is rarely seen in a young woman unless she is a diabetic or a hypertensive. It is important to examine critically the evidence which has been claimed to show the elevated blood pressure is a factor in the female sex but is not a factor in the male sex, since with careful scrutiny of the data, this concept is *not* supported.

THE CHOICE OF CLINICAL MATERIAL FOR THE STUDY OF THE HYPERTENSION FACTOR

The basic question at hand is, "Do persons with habitual elevation in blood pressure level develop *sub-clinical* coronary heart disease at a greater rate than persons without such elevation?" It is a corollary of this question to ask, "Do persons with habitual elevation in blood pressure show a higher attack rate of *clinical* coronary heart disease than do persons without such elevation? If the answer to such questions is in the affirmative, then it would be anticipated that the *average* blood pressure (measured *in advance* of the appearance of clinical coronary heart disease) will be higher for those who do develop clinical coronary heart disease in a specified time interval than for those who do not. Further it would be anticipated that there will be a shift in the distribution of blood pressures toward higher values in the group which later develops clinical coronary heart disease than in the group which does not do so in the same specified time interval. Ideally the appropriate source of clinical material for such a study is a large group of apparently healthy individuals for whom blood pressure measurements are available. Out of an adequately large group of persons there will develop a sub-group with overt clinical manifestations of coronary heart disease in a one-year, two-year, or longer *period*. The outgrowth of an adequately large group of subjects in the clinically-overt coronary disease group during any specified follow-up period is simply a matter of starting with a sufficiently large population sample in [illegible] Fortunately [illegible] ded definitive [illegible] respect to the issue of antecedent blood pressure elevation and coronary heart disease development. Yater[22] has provided the data from one such study and Dawber and co-workers[23] have provided the data from another, the large-scale Framingham Heart Project of the National Heart Institute. The evidence from both these studies is unequivocal and *hence can* provide the *requisite* information without recourse to any of the studies of less definitive character. However, since some of less definitive studies in the clinical literature have influenced medical thinking on this subject and have led *to certain* highly erroneous statements

and conclusions, it is important to review them here, lest the physician be left with the impression that there may be controversial aspects of the problem. It is important to state at the outset that *no contradictory evidence* arises from *any* of the sources of evidence. The apparently contradictory conclusions represent erroneous interpretations of the clinical findings themselves.

As recently as 1954, Wright, Marple and Beck in their book *Myocardial Infarction*[24] *cite the work of Master, Garfield and* Walters[25] as follows, "These authors concluded, therefore, that there was no close relationship between hypertension and coronary artery disease or coronary occlusion in males less than 65 years of age. Hypertension did appear, however, to have an important relationship with coronary occlusion in women." That Wright and co-workers quoted this conclusion without further comment suggests that they were *not prepared to comment on its validity.* Indeed nowhere in their discussion of the relationship of hypertension to coronary heart disease did Wright and co-authors make any definite statement of their own concerning the relationship of these entities. Levine and Brown[26] had long before stated that, "A pre-existing hypertension is probably the most common etiologic factor in the development of myocardial infarction in the majority of cases." The physician reading such reference sources might readily conclude that some question exists as to whether antecedent hypertension exists in persons who develop clinical coronary heart disease, at least for men, or at least for men under *65 years of age. Yet, the evidence from clinical sources* should not lead to an equivocal position on this most important issue. Why, then, does some question appear to exist?

The largest part of the confusion in the literature on this issue arises from two sources.

(1) The arbitrary definition of what constitutes hypertension.

(2) Having established an arbitrary definition of hypertension, the clinician's expectation that some large proportion, preferably over 50%, of cases of myocardial infarction should have had at least this degree of antecedent hypertension.

Neither an arbitrary definition of hypertension nor an

expectation that an arbitrary proportion of myocardial infarction cases would have shown antecedent hypertension by such arbitrary definition is helpful in this problem. The crucial issue was outlined previously, namely, whether or not the myocardial infarction cases showed a distribution of antecedent blood pressures shifted to a higher level and a higher average blood pressure than persons free of clinical coronary heart disease in the same follow-up period For, if such a difference in average blood pressure and distribution of blood pressure values does exist, then it follows unequivocally that blood pressure elevation is associated with sub clinical coronary heart disease and that the blood pressure level can be utilized as a predictive measure with respect to the development of future clinical coronary heart disease To be sure, the greater the difference in the average antecedent blood pressure values between the persons who do develop clinical coronary heart disease and those who do not during the same specified time interval, the more the blood pressure measurement will be helpful in prediction of the risk of future clinical coronary heart disease for currently healthy persons. But no statistical or medical consideration justifies the requirement that any arbitrary proportion of the de novo myocardial infarction cases exceed any arbitrary blood pressure level When analyzed correctly, every reported study known to the present author clearly supports the view that antecedent blood pressure elevation is distinctly associated with the development of sub-clinical coronary heart disease and that the blood pressure is an important predictive measure in determination of the risk of future clinical coronary heart disease for *both men and women at all ages* While some of the reported studies utilized clinical material of somewhat doubtful value, the evidence from them as a whole is so overwhelming as to leave no doubt about the findings and their proper interpretation The chief criticism of the usual clinical material is that the cases of myocardial infarction are either from hospital admissions or from the office practise of the reporting physician In these studies some authors utilized antecedent blood pressure measurements for such cases either from their own office records or from hospital charts The doubt we must entertain centers around the very fact that a measurement

and conclusions, it is important to review them here, lest the physician be left with the impression that there may be controversial aspects of the problem. It is important to state at the outset that *no contradictory evidence* arises from *any* of the sources of evidence. The apparently contradictory conclusions represent erroneous interpretations of the clinical findings themselves.

As recently as 1954, Wright, Marple and Beck in their book Myocardial Infarction[24] cite the work of Master, Garfield and Walters[25] as follows, "These authors concluded, therefore, that there was no close relationship between hypertension and coronary artery disease or coronary occlusion in males less than 65 years of age. Hypertension did appear, however, to have an important relationship with coronary occlusion in women." That Wright and co-workers quoted this conclusion without further comment suggests that they were not prepared to comment on its validity. Indeed nowhere in their discussion of the relationship of hypertension to coronary heart disease did Wright and co-authors make *any definite statement of their own concerning the relationship* of these entities. Levine and Brown[26] had long before stated that, "A pre-existing hypertension is probably the most common etiologic factor in the development of myocardial infarction in the majority of cases." The physician reading such reference sources might readily conclude that some question exists as to whether antecedent hypertension exists in persons who develop clinical coronary heart disease, at least for men, or at least for men under 65 years of age. Yet, the evidence from clinical sources should not lead to an equivocal position on this most important issue Why, then, does some question appear to exist?

The largest part of the confusion in the literature on this issue arises from two sources.

(1) The arbitrary definition of what constitutes hypertension.

(2) Having established an arbitrary definition of hypertension, the clinician's expectation that some large proportion, preferably over 50%, of cases of myocardial infarction should have had at least this degree of antecedent hypertension.

Neither an arbitrary definition of hypertension nor an

persons, taken as representative of the population-at-large, by the same criteria of blood pressure limits (160 mm Hg systolic or 100 mm Hg diastolic or both), such a group of persons at age 58 5 years would be expected to show 28 to 30% with a classification of hypertension. Since Levine and Brown found 40% of their patients to qualify (plus additional cases with *clinical* evidence of pre-existing hypertension) it is clear that in this series, the mean blood pressure was high and the distribution of values shifted

tion. In this group were 194 men (average age 58 9 years) and 80 women (average age 59 7 years). Of the entire group 173 patients, or 63%, were known to have had blood pressures of over 140 mm Hg systolic, or 90 mm Hg diastolic, or both, antecedent to their coronary occlusion. Since the antecedent blood pressure was not known for many patients, the true incidence of pressures above these limits must have been greater than the 63% recorded by Rathe From the Master data it would be anticipated that approximately 57% of individuals of this average age would show blood pressures of over 140 mm Hg systolic, or 90 mm Hg diastolic, or both. Since the Rathe incidence of 63% is a *minimum* value, it appears that his series of patients with clinical coronary heart disease had had antecedent elevation of blood pressures in comparison with those in the population-at-large.

Chambers[27] reported on a series of 100 cases of myocardial infarction (72 males and 28 females). For 85 of these 100 cases the blood pressure during *the pre-infarction* period was known. As criteria for hypertension he required a systolic pressure of 150 mm Hg or more plus a diastolic pressure of 90 mm Hg *or more.* Seventy-four of the 100 cases were known *to have* been hypertensive by these criteria, while for 15 cases the *antecedent* blood pressure was unknown Therefore, *at a minimum,* 74% of his cases were hypertensive *before* the myocardial infarction. From the Master data, utilizing the criterion of diastolic pressure 90 mm Hg or higher, no more than 35% of the population-at-large would be hypertensive (*and this is a less* rigid criterion than that of Chambers) Therefore the 100 case series of Chambers showed a strik-

of the blood pressure for such persons *exists*, especially when we wish to compare such blood pressures with those in the population-at-large. For, if a person has a hospital chart record or an office record of previous blood pressure readings, there must have existed some medical complaint that had led him either to a physician's office or to a hospital, unless he were accustomed to routine periodic medical check-ups. Thus the possibility that such blood pressures are not representative of those in the population-at-large definitely exists, and indeed they may be seriously biassed in the direction of elevated pressures. On the other hand, in some of the reported series of cases antecedent blood pressure records were unavailable for some of the cases of myocardial infarction. In such cases the authors utilized blood pressure readings taken on the patients during their hospitalization for the myocardial infarction itself. This type of blood pressure reading will, for many cases, be lower than the habitual blood pressure the particular person would have shown in the months or years before myocardial infarction, since it is well-known that the blood pressure may fall appreciably (and remain low for a long period) after myocardial infarction. Numerous of the workers were cognizant that in-hospital blood pressures might be biassed, and biassed in the direction of being too low as a measure of the particular patient's habitual blood pressure. Thus, some possible sources of bias exist that might yield too high a blood pressure for the cases of clinical coronary heart disease, whereas others exist that might yield too low a blood pressure. To what extent such biasses cancel each other out in some of the studies reported in the literature is problematical. However, with the necessary reservations in mind, it is worthwhile to consider the major literature reports on the relationship of blood pressure levels with myocardial infarction both in men and women at various ages.

Levine and Brown studied 145 patients with myocardial infarction. Of this group of patients 58 were known to have had pre-existing hypertension, using as a definition of hypertension a systolic pressure of 160 mm Hg. or more or a diastolic pressure of 100 mm Hg or more. The average age for this group of patients was 58.5 years. From the data of Master, Garfield, and Walters, based upon the analysis of data for 74,000 employed

persons, taken as representative of the population-at-large, by the same criteria of blood pressure limits (160 mm Hg systolic or 100 mm Hg diastolic or both), such a group of persons at age 58.5 years would be expected to show 28 to 30% with a classification of hypertension. Since Levine and Brown found 40% of their patients to qualify (plus additional cases with clinical evidence of pre-existing hypertension) it is clear that in this series, the mean blood pressure was high and the distribution of values shifted toward high levels in the persons experiencing myocardial infarction as compared with the population-at-large.

Rathe[27] analyzed the history in 274 cases of myocardial infarction. In this group were 194 men (average age 58.9 years) and 80 women (average age 59.7 years). Of the entire group 173 patients, or 63%, were known to have had blood pressures of over 140 mm Hg systolic, or 90 mm Hg diastolic, or both, antecedent to their coronary occlusion Since the antecedent blood pressure was not known for many patients, the true incidence of pressures above these limits must have been greater than the 63% recorded by Rathe. From the Master data it would be anticipated that approximately 57% of individuals of this average age would show blood pressures of over 140 mm Hg systolic, or 90 mm Hg diastolic, or both. Since the Rathe incidence of 63% is a *minimum value*, it appears that his series of patients with clinical coronary heart disease had had antecedent elevation of blood pressures in comparison with those in the population-at-large.

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ing elevation in blood pressure and a shift to higher values as compared with the population-at-large.

Doscher and Poindexter[28] reported a series of 414 cases of myocardial infarction observed between 1935 and 1948, including 334 men and 80 women. As a criterion for hypertension they required a history of, or an observation post-infarction, of a diastolic pressure of 100 mm Hg or more. Since no history was available for some of the cases and because infarction itself can have lowered observed post-infarction pressures, the incidence of hypertension reported by Doscher and Poindexter would have to be regarded as a minimum value. Since sufficient numbers of cases are available for several age categories for both sexes, comparisons are made in Table V between the hypertension incidence in the Doscher - Poindexter series and the population - at - large data of Master. For each age category and for both sexes the Doscher-Poindexter series shows a striking shift of blood pressures to high values in those persons developing myocardial infarction in comparison with the persons in the population-at-large.

Mintz and Katz[29] reported a series of 572 cases of myocardial infarction from the 1940-1945 experience at Michael Reese Hospital. For 308 of these cases the blood pressure values in the pre-infarction period were known. Of this latter group 188 cases (61%) were known to have had diastolic blood pressures above 90 mm Hg. The average age of the males in their series was 59.2 years; the average age of the females was 62.2 years. From the distribution of males and females in their series and the incidence of hypertension for the two sexes, it is readily calculated that approximately 50% of the men and 86% of the women had antecedent hypertension by their criterion. These values should be compared as follows with the analogous data of Master for the population-at-large, the 50% of men with coronary disease with a value of 35% for men in the population-at-large, the 86% of women with coronary disease with a value of 39% for women in the population-at-large. Clearly, for both sexes, the Mintz and Katz series of cases of myocardial infarction shows a marked shift to high values of the blood pressure for persons later experiencing myocardial infarction.

Master, Garfield and Walters[25] presented data for 554 cases of

TABLE V

INCIDENCE OF HYPERTENSION BY AGE AND SEX IN DOSCHER POINDEXTER SERIES OF MYOCARDIAL INFARCTION CASES

(Criterion of Hypertension, Diastolic Pressure 100 mm Hg or Higher)

Males	30-39 Years	40-49 Years	50-59 Years	60-69 Years	70+ Years
Number of cases	(18 cases)	(85 cases)	(126 cases)	(83 cases)	(20 cases)
Incidence of Hypertension in Myocardial Infarction Cases	11%	29%	33%	42%	35%
Incidence of Hypertension in Population at large (Matched by age)*	3%	6%	11%	15%	Data not available
Females					
Number of cases	(1 case)	(5 cases)	(35 cases)	(27 cases)	(14 cases)
Incidence of Hypertension in Myocardial Infarction Cases	Too few cases	Too few cases	51%	41%	61%
Incidence of Hypertension in Population at-large (Matched by age)*			12%	16%	Data not available

*Population at large data are those of Master, Garfield, and Walters[23]

coronary occlusion in whom the status of antecedent blood pressures was evaluated. By Master's method hypertension is defined, for any age and sex group, as that blood pressure value exceeded only by 2 5% of the persons in the population-at-large. Therefore in comparing his infarction series with the population-at-large, the incidence of hypertension in the latter group by his criteria is always 2 5% The comparison of Master's infarction series with the population-at-large is presented in Table VI. In both sexes, and for every age category where adequate data are available, there is a strikingly greater incidence of hypertension in the myo-

TABLE VI

INCIDENCE OF ANTECEDENT HYPERTENSION IN MYOCARDIAL INFARCTION CASES
(Based upon 554 Cases of Master and Co-workers[31])

Males *Age Group*	*Number of Cases of Myocardial Infarction*	*Incidence of Hypertension in Myocardial Infarction Cases (%)*	*Incidence of Hypertension in Population-at-Large* (%)*
35-39 years	18	16.7%	2.5%
40-44 years	66	25.8%	2.5%
45-49 years	80	27.5%	2.5%
50-54 years	121	28.9%	2.5%
55-59 years	105	25.6%	2.5%
60-64 years	61	31.2%	2.5%
Females			
35-39 years	4	75.0%	2.5%
40-44 years	9	44.4%	2.5%
45-49 years	9	77.6%	2.5%
50-54 years	18	77.8%	2.5%
55-59 years	28	64.4%	2.5%
60-64 years	32	78.2%	2.5%

*All values for the incidence of hypertension in the population-at-large are necessarily 2.5% in this tabulation by virtue of Master's definition of hypertension.

cardial infarction cases than in the corresponding group from the population-at-large. Master, however, focussing on another aspect of the data, drew the opposite conclusion. He pointed out that hypertension (by his definition) was present *only* in 27% of the males. Since this meant that over 70% of men with coronary occlusion had had normal blood pressures, he stated, "The evident conclusion to be drawn is, that there is no very close relationship between hypertension and coronary artery disease and occlusion in the males, at least in those under sixty-five years of age." The really correct evident conclusion is that elevation in blood pressure is *strongly* related to development of coronary occlusion in men at every age investigated. When 27% of the persons who *develop coronary occlusion are characterized by blood pressures* above a specified level in contrast with 2.5% of the persons who do not develop coronary occlusion in the same time period, we have at hand a fabulously strong association between coronary occlusion and antecedent elevation in blood pressure. The error in Master's reasoning lies in choosing an arbitrary blood pressure value (that above which lie only 2.5% of the population) and then

being disturbed by the fact that only 27% of the coronary occlusion cases had antecedent pressures above this level The real comparison is between 27% and 2.5%, rather than between 27% and 100%.

While it is clear from these several clinical series of myocardial infarction cases that antecedent blood pressure elevation characterizes persons developing clinical coronary heart disease, there remain the possible sources of bias described previously. We may therefore consider the evidence from two studies where such sources of bias do not exist One such study, the Framingham study of the National Heart Institute, has recently been reported by Dawber, Moore, and Mann[23]. This is a continuing epidemiological study of the extent of development of new cardiovascular disease in a cross-section of the population of the town of Framingham, Massachusetts. All the subjects in this cross-section of the population are examined by clinical and laboratory methods every two years and a careful followup is in progress continually to ascertain the development of such new events as myocardial infarction or other forms of coronary heart disease. The experience with four years of follow-up in this study yielded definitive results with respect to the relationship of blood pressure with the subsequent evolution of clinical coronary heart disease. There were 898 men between the ages of 45 and 62 years who represented the population at risk during the reported four year follow-up period At the time of the *initial* examination *none* of these 898 men showed evidence, clinical or laboratory, of definite coronary heart disease. During the four year period 48 of the men developed what were regarded as definite manifestations of clinical coronary heart disease, including one or more of the following entities. myocardial infarction, coronary occlusion, angina pectoris, myocardial fibrosis, or electrocardiographic evidence of myocardial infarction The original group of 898 men can be subdivided on the basis of blood pressure into two major groups, the normotensives on initial examination and those with varying degrees of hypertension, borderline or definite. For purposes of definition of normotension, Dawber and co-workers used the criterion that left arm blood pressures had to be below 140/90 mm Hg on independent observations by two physicians All other

subjects fit into one or another category, such as borderline hypertension, definite hypertension, and possible or definite hypertensive heart disease. The normotensive group, constituting 310 men, developed 8 cases of new events classified as manifestations of clinical coronary heart disease during the four year follow-up period.* The remaining group (various degrees of hypertension by their criteria), constituting 541 men, developed 40 cases of new events classified as manifestations of clinical coronary heart disease during the four year follow-up period. Thus for the "normotensive" group, the incidence rate of de novo clinical coronary heart disease was 26 cases per 1000 persons at risk over the four year period, whereas for the "hypertensive" group the incidence rate of de novo clinical coronary heart disease was 74 cases per 1000 persons at risk over the same time period. This difference in attack rates of de novo clinical coronary heart disease is significant and clearly supports the concept that elevation in blood pressure increases the risk of future clinical coronary heart disease. Stated otherwise, this evidence links elevation in blood pressure with the *sub-clinical* phase of coronary heart disease and indicates that the blood pressure is one predictive measure for ascertaining the risk a person carries for passing from the sub-clinical to the clinical phase of coronary heart disease.

Another wholly separate study provides evidence completely consistent with that derived from the Framingham study. This is the analysis of Yater and co-workers[22] of 542 men who survived a documented myocardial infarction or who died of coronary heart disease while in the Armed Services. The average age of this group was approximately 33 years. For these men who developed their clinical coronary heart disease while in the Armed Service there was available to Yater the blood pressure values at induction examination, at which time all the men were free of recognizable clinical coronary heart disease. In order to have a control group whose blood pressures had been measured under as nearly identical conditions as for the coronary heart disease group, Yater utilized the induction blood pressures for 213 men who were service-connected amputees or who were otherwise wounded, none of

*Forty seven of the 898 men were normotensive, but had a history of cerebro vascular accident of rheumatic heart disease. These are excluded from analysis.

whom had overt coronary heart disease. The systolic pressures were found to be above normal (utilizing a criterion of 139 mm Hg systolic as the upper limit of normal) in 27.9% of the men (18 to 39 years of age) who subsequently developed clinical coronary heart disease contrasted with 8.9% of the men in the Army control group. Thus there was a three-fold increase in the incidence of high systolic pressures at Army induction for those who subsequently developed clinical coronary heart disease in comparison with those who did not. The same type of trend was evident for the diastolic blood pressures. Whereas 19.1% of the men who subsequently developed clinical coronary heart disease had shown diastolic blood pressures above 90 mm Hg at induction, only 3.8% of the Army control group had shown diastolic pressures above 90 mm Hg at induction. There was, therefore, a five-fold increase in incidence in prior diastolic blood pressure elevation above 90 mm Hg in the coronary disease group in comparison with the control group. Clearly, the Yater data indicate that elevation both in systolic and diastolic blood pressures characterizes the men in the 18-39 year age group who go on to develop clinical coronary heart disease in comparison with those men of the same age group who remain free of overt clinical coronary heart disease during the same time period.

The combination of the Framingham evidence with Yater's evidence covers the age span for men from 18 to 62 years of age. Over this entire age span the relationship between antecedent blood pressure elevation and later development of clinical coronary heart disease is known to be *valid*. *Yet this* is essentially the age span in men for which Master had concluded that there was no "close" relationship between hypertension and the subsequent development of clinical coronary heart disease. No contradiction whatever exists among the findings of Dawber at Framingham, of Yater in the Army, and of Master in his series. All show that blood pressure elevation is associated with a sizably higher attack rate of future clinical coronary heart disease. Master's difficulty resided in his expectation that an *arbitrarily* large percentage of men who subsequently develop clinical coronary heart disease must have a blood pressure elevation of *arbitrary* degree if the blood pressure is to be important. No real justifi-

subjects fit into one or another category, such as borderline hypertension, definite hypertension, and possible or definite hypertensive heart disease. The normotensive group, constituting 310 men, developed 8 cases of new events classified as manifestations of clinical coronary heart disease during the four year follow-up period.* The remaining group (various degrees of hypertension by their criteria), constituting 541 men, developed 40 cases of new events classified as manifestations of clinical coronary heart disease during the four year follow-up period. Thus for the "normotensive" group, the incidence rate of de novo clinical coronary heart disease was 26 cases per 1000 persons at risk over the four year period, whereas for the "hypertensive" group the incidence rate of de novo clinical coronary heart disease was 74 cases per 1000 persons at risk over the same time period. This difference in attack rates of de novo clinical coronary heart disease is significant and clearly supports the concept that elevation in blood pressure increases the risk of future clinical coronary heart disease. Stated otherwise, this evidence links elevation in blood pressure with the *sub-clinical* phase of coronary heart disease and indicates that the blood pressure is one predictive measure for ascertaining the risk a person carries for passing from the sub-clinical to the clinical phase of coronary heart disease

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*Forty seven of the 898 men were normotensive, but had a history of cerebro vascular accident of rheumatic heart disease These are excluded from analysis

Whatever the merits of this possible explanation for the association of elevation in blood pressure with a higher frequency of clinical coronary heart disease, it has, contrary to many opinions, *no* bearing upon the utility of the blood pressure measurement as a predictive measure in assessing the risk of future clinical coronary heart disease. The data reviewed in this chapter establish conclusively that the average elevation in blood pressure is present *during the sub-clinical* phase of coronary heart disease, and for a period of several years *before* the evolution of clinically-overt coronary heart disease This is the crucial issue with respect to the question of utility of the blood pressure as a *predictive* criterion. Whether the blood pressure is a factor in acceleration of the coronary disease or whether the coronary disease results in the blood pressure rise as a compensatory mechanism, the existence of the pressure elevation during the sub-clinical phase of coronary heart disease *necessarily* means that the measurement of blood pressure is of value in assessing the development of coronary heart disease, and hence the risk of serious future clinical consequences. The possibility of prevention or therapy of coronary heart disease is, of course, a matter apart from such considerations If the blood pressure elevation is truly part of a compensatory mechanism to increase coronary artery blood flow, then efforts to lower blood pressure as a means of preventing or treating coronary heart disease would be unwise. On the other hand if the blood pressure elevation is a predisposing factor to coronary heart disease there would exist excellent justification for attempting to lower the blood pressure in the effort to prevent or treat clinical coronary heart disease. This question cannot be decided from the observation of the association of sub-clinical coronary heart disease with blood pressure elevation Direct clinical preventive and therapeutic experiments are necessary supplements toward this end. However, all the indirect evidence supports the view that the blood pressure elevation accelerates the development of the coronary heart disease rather than that the coronary heart disease causes the elevation in pressure. The experimental animal data point very strongly to the probability that the way in which blood pressure elevation comes to be associated with coronary heart disease is

cation exists for such a view. The extent of the differences in attack rate of clinical coronary heart disease for persons with high blood pressure versus those with low blood pressure is in reality quite phenomenal and provides predictive information of major value. Exactly how these differences are to be utilized in the advance prediction of future clinical coronary heart disease will be detailed in Chapter V.

To be sure, the data from all the sources of evidence show clearly that blood pressure values above some arbitrary high level are not *prerequisite* to the development of clinical coronary heart disease. Clinical coronary heart disease can and does develop in persons with moderate or even low blood pressures, but the frequency of its occurrence is strikingly lower than in persons with elevation in blood pressure. Perhaps another feature which Master found disturbing was that antecedent elevation in blood pressure is much more frequently found in women who develop clinical coronary heart disease than in men who do so. This finding in no way negates the importance of the blood pressure level for the development of clinical coronary heart disease in men at any age. There exist good and sufficient reasons why hypertension should be expected to be a more frequent finding among women who develop clinical coronary heart disease than among men who develop this disease. The explanation of this phenomenon requires consideration of the blood pressure findings together with the lipoprotein findings and the manner in which risk of coronary heart disease is related to both factors operating simultaneously. Therefore detailed consideration of the difference in incidence of hypertension between men and women who develop coronary heart disease is presented in Chapter VIII, where such risk calculations are explained.

There are some, writing on the subject of coronary heart disease, who raise the question as to whether the elevation in blood pressure observed in those who go on more frequently to develop clinical coronary heart disease may not be a protective phenomenon. Thus Yater suggested the possibility that the hypertension which precedes clinical coronary heart disease may be part of an effort to compensate for reduced coronary arterial blood flow by an increase in the pressure in the arterial tree.

viduals at a particular age are evaluated both with respect to lipoprotein levels and blood pressure levels and then followed for a period of years, a sub-group will develop which shows clinically-manifest coronary heart disease. This sub-group, we now know, would have originally been characterized both by elevation in lipoprotein levels and in blood pressure levels. From the extent of correlation of blood lipoprotein levels and blood pressure levels it can be calculated that a certain blood pressure elevation would be expected in the sub-group with clinical coronary heart disease, even if the blood pressure provided *no* independent predictive information. However direct test of such evidence by the author and his colleagues[17] showed that there *is* an elevation of blood pressure *over* and *above* that expected from the correlation of blood lipoproteins and blood pressure. *Hence the blood pressure does* provide information of predictive value concerning future clinical coronary heart disease *in addition* to that provided by lipoprotein analysis An alternative manner of considering the test for independence may be described. If the sub-group which does develop clinical coronary heart disease is matched with random cases from the population-at-large such that the lipoprotein levels are equivalent for both groups, is the blood pressure *still* elevated in the group with clinical coronary disease in comparison with the lipoprotein-matched controls? Direct test of this showed that the blood pressures were still elevated in the coronary disease group even when the two groups were matched upon lipoprotein levels. This is clear evidence that the blood pressure measure provides information additional to, and independent of, that provided by lipoprotein measurement. Hence, in any consideration of risk of future clinical coronary heart disease both factors, blood lipoprotein level and blood pressure level, must be evaluated, or valuable information will necessarily be lost

via the effect of hypertension in acceleration of the coronary arteriosclerotic process. The increased arteriosclerosis in humans in regions of the vascular tree subjected to excessive pressure is consistent with the animal data, and not at all supportive of the concept that the blood pressure elevation is a compensatory phenomenon. Altogether the indirect evidence suggests that the blood pressure elevation, in addition to being predictive of clinical coronary heart disease by virtue of its statistical association with it, in all likelihood abets the development of coronary heart disease.

INDEPENDENCE OF THE INFORMATION PROVIDED BY THE BLOOD PRESSURE

In Chapter III it was shown that conclusive evidence is available to show that the blood low-density lipoproteins are, on the average, elevated during the sub-clinical phase of coronary heart disease, and hence blood lipoprotein measurements have predictive implications for future clinical coronary heart disease. In this chapter it has been shown that similar conclusive evidence is at hand that information of predictive value for clinical coronary heart disease is obtained through the measurement of the blood pressure of persons in advance of any overt manifestations of coronary heart disease. Do these two sets of measurements provide *independent* information concerning the risk of future clinical coronary heart disease? If *no* independent information were provided by blood pressure measurement over and above that provided by lipoprotein measurement, this would mean that any predictive information from blood pressure measurement must have arisen solely through a correlation of elevation of blood pressure with elevation in blood lipoprotein levels In this case the blood pressure measurement would be of no predictive value for future clinical coronary heart disease once the lipoprotein levels were known There does indeed exist a low-order correlation between lipoprotein levels and blood pressure levels. However, this is not sufficient evidence upon which to base the decision as to whether the blood pressure measurement provides *independent* predictive information. The critical test for this point is made in the following manner. If a large group of indi-

develop clinical coronary heart disease in some specified time interval, there simply are not enough data available today to make this sort of exact evaluation. However what information is available makes for a tremendous amount of predictive power, a power that can be used now in a sensible program designed for the prevention of coronary heart disease.

For illustrative purposes in the demonstration of how risk is directly related to the measurement of any particular variable that is elevated in those individuals going on to develop clinical coronary heart disease compared with the population out of which they arise, the data concerning the S_f0-12 lipoprotein measurement in 40-49 year old men will be utilized here. Also because the data are available for a much larger number of cases, the S_f0-12 measurement for a large series of cases with documented clinical coronary heart disease will be used instead of the smaller series of de novo cases of myocardial infarction arising in previous well individuals This is perfectly justifiable since the levels of the various lipoprotein classes characterizing the de novo cases of myocardial infarction were shown in a previous discussion, (page 57), to be quite comparable with those characterising cases with already-established clinical coronary heart disease. Available also are the distributions of the S_f0-12 lipoproteins in age- and sex-matched controls from the population-at-large. If the coronary cases had arisen out of a large series of such age- and sex-matched controls in overt health, we would have the S_f0-12 distribution of values for the original population sample and the values which characterize those individuals who became cases of clinical coronary heart disease at some future time, whatever that time might be, e g, 1 year, 2 years or 3 years later. Listed in Table VII is the distribution of S_f0-12 values, assuming a base population of 10,000 subjects evaluated Actually this distribution was determined on 525 subjects and simply multiplied by a conversion factor to calculate what the numbers would be in each S_f0-12 lipoprotein category for an over-all group of 10,000 subjects. One has, therefore, in Table VII, for each small range of S_f0-12 values, a number which represents the number of individuals found in the population-at-large who would show this S_f0-12 lipoprotein value upon measurement. As is to be expected, most of

Chapter V

THE PREDICTION OF FUTURE CLINICAL CORONARY HEART DISEASE

EVIDENCE is available which indicates conclusively that two independent factors characterize the individual developing excessive sub-clinical coronary heart disease. These are the level of certain blood lipoproteins and the level of the diastolic blood pressure. Both for the lipoprotein level and the blood pressure, it has been proven beyond reasonable doubt that the abnormality manifests itself during the sub-clinical phase of coronary disease, namely, before the evolution of the disease into the clinically-overt state. How is this information to be used in the prediction of clinical coronary heart disease risk in otherwise healthy individuals? It can be readily demonstrated through simple arithmetic that, when a measurement (any measurement) shows a higher average value and a shift in the distribution to higher *values for those individuals who later go on to develop clinical* coronary heart disease, such a measurement is directly capable of being translated into a prediction of the risk of future clinical coronary heart disease. At the outset it must be emphasized vig*orously that what can be predicted is the risk of future clinical* coronary heart disease. Much confusion needlessly centers around this point. There is no intent to state or claim that prediction is possible, for a particular individual, that he *will* develop clinical coronary heart disease in any specified time interval. This would not be a risk, but a forecast of future certainty. By risk is meant the probability, or likelihood, of developing coronary heart disease, rather than the certainty involved in naming the day or year a particular individual will develop coronary heart disease. While the physician might like to have unequivocal information concerning whether or not a particular subject will

of our base population for which a risk calculation can be made. If there are 31 cases of coronary disease below the median value arising out of 5000 individuals, this is a coronary disease attack rate of 6.2 per thousand individuals. On the other hand, since there are 82 cases of clinical coronary disease arising out of the 5000 individuals with levels above the median value, this represents an attack rate of 16.4 per thousand, which is 2.65 times as high as the value for the segment of the base population below the median value. Therefore *without any further information* concerning such individuals, it is possible to state that if a person is measured with respect to S_f0-12 lipoprotein level and if his level is above the median value, he is 2.65 times as likely to develop clinical coronary heart disease in some specified time interval as he would be had his S_f0-12 lipoprotein level been below the median value. It is to be remembered that this statement holds when such other variables as age and sex are matched. There is no inference that prediction would be handled in this simple manner if a 20 year old man were to be compared with a 65 year old woman. The problem of dealing with the age and

TABLE VIII

DISTRIBUTION OF S_f0-12 LIPOPROTEIN LEVELS IN 113 CASES OF DOCUMENTED MYOCARDIAL INFARCTION (MEN, AGE 40-49 YEARS)

Range of S_f0-12 Lipoprotein Levels mg/100ml	*Number of Men in Each S_f0-12 Category*
Less than 224	2
224-267	4
268-311	6
312-356	10
357-401	16
402-446	24
447-491	24
492-535	15
536-580	8
581 or higher	4
TOTAL GROUP	113

Median S_f0-12 Lipoprotein Level = 456 mg/100ml

the individuals show values near the median for the S_f0-12 lipoprotein level for 40-49 year old males (average age = 44.5 years), which is 381 mg/100ml. Listed in Table VIII is the corresponding distribution of S_f0-12 lipoprotein levels for the 113 cases of clinical myocardial infarction which can be said to have developed out of a population comparable to that shown in Table VII in a time period such as two to three years. The simplest approach to translation of these two tables of values into predictive terms would be to consider values above and below the median value of the S_f0-12 lipoproteins for the base population. For this base population of 10,000 persons the definition of the median value implies that there will be 5000 individuals with S_f0-12 lipoprotein levels above that value and 5,000 individuals with levels below that median value. If we now direct attention to the cases of myocardial infarction arising out of such a base population and total up the number of cases below this same median value of 381 mg.%, we find there are 31 values below this level and 82 values above this level. Therefore we have a two-fold split

TABLE VII

DISTRIBUTION OF S_f0-12 LIPOPROTEIN LEVELS IN AN OVERTLY HEALTHY BASE POPULATION OF 10 000 MEN (AGE 40-49 YEARS)

Range of S_f0-12 Lipoprotein Levels (mg/100ml)	*Number of Men in Each S_f0-12 Category*
Less than 224	362
224-267	476
268-311	1143
312-356	1791
357-401	2115
402-446	1980
447-491	1372
492-535	514
536-580	171
581 or higher	76
TOTAL GROUP	10,000

Median S_f0-12 Lipoprotein Level = 381 mg/100ml
S_f0-12 Level separating lowest from second lowest quarter of group = 327 mg/100ml
S_f0-12 Level separating third quarter from highest quarter of group = 439 mg/100ml

process further allows the construction of a table of 10 individual categories relating risk of future clinical coronary heart disease to S_f0-12 lipoprotein levels. Such a risk evaluation for various S_f0-12 lipoprotein levels is presented in Table IX, where the risk for the lowest S_f0-12 level is arbitrarily set at 1.0, and where all other risk values are expressed in comparison with this value. Without any further information about the persons involved, such a table can be used to determine the relative risk of one individual versus another developing future clinical coronary heart disease in a specified time interval Many misleading statements have emanated from some writers, who have stated that this type of risk information holds true for groups but does not apply to the individual. Such reasoning is entirely erroneous. A *risk* is a value that has meaning *for an individual.* The error arises from the fact that some persons are confusing the *risk* of future clinical coronary heart disease with an absolute statement of the day, week, or month that this particular individual will develop clinical coronary heart disease. Let us review what is meant by risk. Suppose that two groups, each constituting one thousand individuals, are considered, the first group all having S_f0-12 lipoprotein levels of 200 mg/100ml and the second group

TABLE IX

RELATIVE RISK OF MYOCARDIAL INFARCTION AT VARIOUS S_f0 12 LIPOPROTEIN LEVELS

S_f0 12 Lipoprotein Level (in mg/100ml)	*Relative Risk of Development of Myocardial Infarction (All risks referred to the risk at 200 mg/100ml S_f0-12 lipoproteins set at 1.00)*
200	1 00
250	1 06
300	1 15
350	1.22
400	1.50
450	2 30
500	3 90
550	6.30
600	9 75
650	13.2

the sex factors will be considered later (Chapters VII and VIII).

It is quite evident that such a two-fold prediction table can readily be extended. There is no reason to limit sub-division of the base population with respect to standard S_f0-12 level to just a two-fold split above and below the median value. The base population can be sub-divided still further into the lowest quarter, the next quarter, the third quarter, and the highest quarter of the group of individuals with respect to S_f0-12 levels, yielding 2500 individuals in each of the four categories. The S_f0-12 lipoprotein level that separates the lowest quarter from the second lowest quarter *is 327 mg/100ml, the level that separates the* third quarter from the highest quarter is 439 mg/100ml, and the median value, 381 mg/100ml separates the two intermediary quarters. From the overall group of cases of coronary disease, *those with S_f0-12 lipoprotein levels below the value separating* the lowest quarter from the second lowest quarter come to 14 cases. In the second lowest quarter there are 17 cases, in the third quarter there are 25 cases, and in the highest quarter there are 57 cases. Now it is possible to compare the risk of future clinical coronary heart disease for individuals in any one quarter with the risk for individuals in any other quarter. If, in the lowest quarter, there are 14 cases arising out of 2500 people, then the coronary disease attack rate is 5.6 cases per thousand persons at risk, for the second quarter the rate is 6 8 per thousand, for the third quarter the rate is 10.0 per thousand, and for the highest quarter the rate is 22.8 per thousand. Comparison of the attack rate for any quarter with that for any other quarter provides immediately the relative risk of future clinical coronary heart disease carried by persons in these categories simply on the basis of S_f0-12 lipoprotein levels.

It is quite evident that, with respect to the S_f0-12 lipoprotein measurement, the base population could have been subdivided into ten segments, each representing an interval of *S_f0-12 lipoprotein levels from the lowest ten percent of the population* up through to the highest ten percent. Then by counting the number of cases of clinical coronary disease in each such segment, calculation of the number of cases per thousand persons at risk for each segment *is readily possible.* Carrying such a

process further allows the construction of a table of 10 individual categories relating risk of future clinical coronary heart disease to S_f0-12 lipoprotein levels. Such a risk evaluation for various S_f0-12 lipoprotein levels is presented in Table IX, where the risk for the lowest S_f0-12 level is arbitrarily set at 1.0, and where all other risk values are expressed in comparison with this value. Without any further information about the persons involved, such a table can be used to determine the relative risk of one individual versus another developing future clinical coronary heart disease in a specified time interval. Many misleading statements have emanated from some writers, who have stated that this type of risk information holds true for groups but does not apply to the individual. Such reasoning is entirely erroneous. A *risk* is a value that has meaning *for an individual.* The error arises from the fact that some persons are confusing the *risk* of future clinical coronary heart disease with an absolute statement of the day, week, or month that this particular individual will develop clinical coronary heart disease. Let us review what is meant by risk. Suppose that two groups, each constituting one thousand individuals, are considered, the first group all having S_f0-12 lipoprotein levels of 200 mg/100ml and the second group

TABLE IX

RELATIVE RISK OF MYOCARDIAL INFARCTION AT VARIOUS S_f0 12 LIPOPROTEIN LEVELS

S_f0 12 Lipoprotein Level (in mg/100ml)	*Relative Risk of Development of Myocardial Infarction (All risks referred to the risk at 200 mg/100ml S_f0-12 lipoproteins set at 1.00)*
200	1.00
250	1.06
300	1.15
350	1.22
400	1.50
450	2.30
500	3.90
550	6.30
600	9.75
650	13.2

all having S_f0-12 lipoprotein levels of 500 mg/100ml. The data in Table IX indicate that the relative risk of future coronary heart disease for members of the high group is 3.90 times that of the low group. What this means is that if the 1000 individuals with low S_f0-12 lipoprotein values and the thousand individuals with the high S_f0-12 values were in apparent clinical health (which means that they are in the sub-clinical phase of coronary heart disease) and if both groups were observed for a time period such as two years, clinical coronary heart disease would develop in some members of both groups. If, out of the thousand individuals with the lowest S_f0-12 levels, there developed 10 cases of clinical coronary heart disease, then the relative risk table means that out of the group of 1000 individuals with the high S_f0-12 levels there would be 3.90 times ten, or 39 cases of clinical coronary heart disease. Obviously it is true that even for the group with high lipoprotein levels *most* individuals do not develop *clinical* coronary heart disease in a *short specified time interval* such as two years, but this represents no erroneous diagnosis of the *risk* for such persons. No false assessment of a person's chance of development of coronary heart disease is represented by this fact. It is simply inherent in the nature of a risk calculation that many persons will escape the disease even though they are individually characterized by a very high risk of such disease compared with other persons.

In an entirely analogous manner one could treat the S_f12-20 lipoprotein measurement to calculate a coronary heart disease risk value that corresponds with each and every level of the S_f12-20 lipoproteins, without any consideration of any other lipoprotein classes or blood pressure, provided considerations are limited to age- and sex-matched individuals Further, one could separately calculate a table for S_f20-100 lipoprotein level versus risk of clinical coronary heart disease and for S_f100-400 lipoprotein level versus risk of such disease. Additionally, similar risk calculations could readily be made for the diastolic blood pressure alone in a fashion exactly analogous to that outlined in detail for the S_f0-12 lipoproteins. Proceeding in this manner, one would have five separate measurements and five separate risk calculations concerning an individual. A particular person might be

twice as high as the average in terms of risk of coronary heart disease because of his S_f0-12 lipoprotein level but might be four times as high as the average because of his S_f12-20 lipoprotein level, etc Clearly, having five separate risk values to consider without a method for weighing the relative importance of each of these separate risk estimates would be very unwieldy and difficult to handle in clinical practice. Therefore it is necessary to weld the separate sources of risk information together into some composite measures which best express the overall relative risks of any two individuals with respect to the development of future clinical coronary heart disease This problem may be approached in two stages, first, to unify all the lipoprotein risk calculations, namely, to get together in one composite measure of risk that information that derives from S_f0-12, 12-20, 20-100 and 100-400 lipoprotein measurements, and second, to evaluate the risk separately arising from blood pressure values. Finally, it is essential to combine these two risk evaluations into a single composite risk estimate which takes into account all the available information. It is important to re-emphasize here that the reason why all the four separate lipoprotein classes must be taken into account is that each class provides information independent of all the others with respect to coronary disease risk Each class of lipoproteins is involved in the progression of sub-clinical coronary heart disease and hence contributes to the risk of ultimate clinical coronary heart disease If knowledge of the level of one lipoprotein class provided the level of the others, then measurement of any one of the lipoprotein classes would suffice for present purposes. However, it is well-known that a person may be high in S_f0-12 lipoproteins but low in all the other three lipoprotein classes, whereas some other person may be equally high in S_f0-12 lipoproteins and high in one or more of the other three classes. The latter person carries a higher risk of future clinical coronary disease than does the former The human population is so constituted that practically any combination of S_f0-12, 12-20, 20-100 and 100-400 lipoproteins is possible and does occur. Hence the best evaluation of a person with respect to the risk of future clinical coronary heart disease is to be obtained by a combination of the evaluation that derives from each of the four classes sep-

all having S_f0-12 lipoprotein levels of 500 mg/100ml. The data in Table IX indicate that the relative risk of future coronary heart disease for members of the high group is 3.90 times that of the low group. What this means is that if the 1000 individuals with low S_f0-12 lipoprotein values and the thousand individuals with the high S_f0-12 values were in apparent clinical health (which means that they are in the sub-clinical phase of coronary heart disease) and if both groups were observed for a time period such as two years, clinical coronary heart disease would develop in some members of both groups. If, out of the thousand individuals with the lowest S_f0-12 levels, there developed 10 cases of clinical coronary heart disease, then the relative risk table means that out of the group of 1000 individuals with the high S_f0-12 levels there would be 3.90 times ten, or 39 cases of clinical coronary heart disease. Obviously it is true that even for the group with high lipoprotein levels *most* individuals do not develop clinical coronary heart disease in a short specified time interval such as two years, but this represents no erroneous diagnosis of the *risk* for such persons. No false assessment of a person's chance of development of coronary heart disease is represented by this fact. It is simply inherent in the nature of a risk calculation that many persons will escape the disease even though they are individually characterized by a very high risk of such disease compared with other persons.

In an entirely analogous manner one could treat the S_f12-20 lipoprotein measurement to calculate a coronary heart disease risk value that corresponds with each and every level of the S_f12-20 lipoproteins, without any consideration of any other lipoprotein classes or blood pressure, provided considerations are limited to age- and sex-matched individuals. Further, one could separately calculate a table for S_f20-100 lipoprotein level versus risk of clinical coronary heart disease and for S_f100-400 lipoprotein level versus risk of such disease. Additionally, similar risk calculations could readily be made for the diastolic blood pressure alone in a fashion exactly analogous to that outlined in detail for the S_f0-12 lipoproteins Proceeding in this manner, one would have five separate measurements and five separate risk calculations concerning an individual. A particular person might be

100 cases, where the mean value of each lipoprotein class is not as stabilized as it would be with a much larger series of cases, the precise value of the weighting factors is not stably evaluated. It is to be anticipated that the weighting factor determined for each class might fluctuate if studied in one series versus another and might fluctuate some as additional cases are added to the overall series. Because of this sensitivity of the weighting factor to the exact difference in mean value for any lipoprotein class in the coronary and non-coronary cases, it was decided to reduce this sensitivity by combining the S_f12-20 plus S_f20-100 plus S_f100-400 lipoproteins into one composite band and to derive a weighting factor for this band relative to the S_f0-12 band of lipoproteins as a first step. At some future time it will be desirable to have specific weighting factors for each of the lipoprotein sub-classes, but for the present, within the limits imposed by the size of the series of cases studied, it has been decided not to attempt to determine the weighting factor for all the separate bands. The application of the analysis of Fisher to coronary disease cases in men of the age range of 40-50 years had led to a weighting factor for the S_f12-400 band of lipoproteins of approximately 1.75 times that for the S_f0-12 lipoproteins[31]. Therefore, instead of combining the S_f0-12 lipoprotein measurement directly with the S_f12-400 lipoprotein measurement to obtain a composite value, one should first multiply the number of milligrams per 100 ml of S_f12-400 lipoproteins by 1.75 before adding it to the number of milligrams per 100 ml of S_f0-12 lipoproteins. In order to reduce the composite values obtained to a composite value of convenient dimensions, all values are arbitrarily divided by ten. (This is really equivalent to use of centigrams per 100 ml instead of milligrams per 100 ml.) This composite value of the S_f0-12 lipoprotein level plus 1.75 times the S_f12-400 lipoprotein level had been designated as an *Atherogenic Index, or A.I. value*[31]. This A.I. value *need imply nothing* with respect to arteriosclerosis or atherogenesis, but simply is a composite value expressive of the weighted *importance* assigned to each of the lipoprotein classes with respect to coronary heart disease. To be sure, the name, A.I. value, or Atherogenic Index value, was chosen because it was strongly surmised that it had to do with atherogenesis

arately. If each lipoprotein class were exactly equal in importance with respect to the development of coronary heart disease, that is, if one milligram percent of S_f0-12 lipoproteins were equivalent in its effect to one milligram percent of S_f12-20, or one milligram percent of S_f20-100, or one milligram percent of S_f100-400 lipoproteins, there would be a very simple procedure available for rating an individual. Simple addition of the values for the S_f0-12, 12-20, 20-100 and 100-400 lipoprotein levels to yield the S_f0-400 level could be performed. Then in a manner similar to that described above for the S_f0-12 lipoproteins the risk of future coronary heart disease as related to the S_f0-400 level could be calculated. This simplest approach of assuming that each milligram percent of every lipoprotein class means the same thing as each milligram percent of any other lipoprotein class would be certainly a step in the right direction for producing a composite risk estimate. However, there exist methods for treating this problem a little more critically instead of *assuming that each milligram percent of a particular lipoprotein class* is equivalent to one milligram percent of any other class with respect to coronary heart disease. The British statistician, Fisher[30], has developed a statistical method for dealing with problems such as this, which allows calculation of a weighting factor to be applied to each of the measurements before adding the separate measurements. For example, should Fisher's method indicate that S_f12-20 lipoproteins deserve a weighting factor of 2 compared with a weighting factor of 1 for S_f0-12 lipoproteins, that S_f20-100 lipoproteins deserve a weighting factor of 2½, and that S_f100-400 lipoproteins, a weighting factor of 3, then instead of adding together the milligrams percent directly, one would add the milligrams percent of S_f0-12 plus 2 times the milligrams percent of S_f12-20 plus 2½ times the milligrams percent of S_f20-100 plus 3 times the milligrams percent of S_f100-400 to obtain a composite value that best characterizes the individual. The precise values of the weighting factors for each lipoprotein class are *somewhat sensitive to the magnitude of the difference* in average lipoprotein levels between coronary disease and non-coronary disease cases for each of the lipoprotein classes. Therefore with a small series of cases of coronary disease, even a series of

the S_f0-12 lipoproteins. The Atherogenic Index value, or A.I. value, is calculated for each person from his lipoprotein levels. This can be done for the base population of 10,000 (40-49 year old) men in apparent health as discussed previously and can be done for a series of coronary disease cases that would in time grow out of such a base population. The persons in both the original healthy series and the clinical coronary disease series can be ranked in ten categories, from the Atherogenic Index values for the lowest 10% of the healthy group up through the values for the highest 10% of the healthy group. These values are categorized in Tables X and XI From these data the number of coronary disease cases per 1000 healthy persons in each Atherogenic Index category is immediately available. The ratio of the number of coronary disease cases per thousand healthy men for any two Atherogenic Index categories is *directly* the relative risk of clinical coronary heart disease for these categories. Such relative risks are presented in Table XII.

The Atherogenic Index composite risk calculation takes into account all the information from the various lipoprotein measurements, but does not take into account the blood pressure information The blood pressure will be considered below. At the moment consideration must be given to the problem of how

TABLE X

RANGES OF ATHEROGENIC INDEX VALUES EACH COMPRISING 1000 MEN OUT OF A BASE POPULATION OF 10 000 OVERTLY HEALTHY MEN (AGE 40-49 YEARS)

Atherogenic Index Categories Each Containing 1000 Men	*Range of Atherogenic Index Values*
Lowest category of 1000 men	Below 48
2nd category of 1000 men	49 55
3rd category of 1000 men	56-61
4th category of 1000 men	62-67
5th category of 1000 men	68 73
6th category of 1000 men	74 78
7th category of 1000 men	79 87
8th category of 1000 men	88 96
9th category of 1000 men	97 108
Highest category of 1000 men	Above 109

in the coronary arteries. However, since this entire thesis is being developed without any need to refer to atherogenesis, the A.I. value can *simply be defined* as the S_f0-12 lipoprotein level plus 1.75 times the S_f12-400 lipoprotein level. As an illustration of the calculation of Atherogenic Index values, the following example is considered. If a person shows 365 mg/100ml of S_f0-12 lipoproteins and 150 mg/100ml of S_f12-400 lipoproteins, the Atherogenic Index value will be equal to 365 plus 1.75 times the 150, all divided by ten, which yields an A.I. value of 63 units. Such a composite value is a step closer to the best composite value than that obtained by simply adding all the lipoprotein measurements together because it takes into account the weighted importance of the S_f12-400 lipoproteins. It is to be anticipated that when a larger series of coronary disease cases is studied, and especially when a large series has arisen out of an original base population of individuals, and the mean difference for each of the lipoprotein classes is fixed more precisely for the coronary disease cases versus the matched controls, the weighting factor of 1.75 for the S_f12-400 lipoproteins versus 1.0 for the S_f0-12 lipoproteins may change some. It may go down from 1.75 or it may go up some. However none of the conclusions derived from utilization of the 1.75 value will be appreciably altered by such a shift in the value. The crucial issue to understand is that, since a person derives his risk of future clinical coronary disease from all four classes of lipoproteins S_f0-12, S_f12-20, S_f20-100, and S_f100-400), they must *all* be considered. For the present time the best weighting factor for S_f12-400 lipoproteins appears to be approximately 1.75 times that for the S_f0-12 lipoproteins, but the composite value derived thereby is not critically affected for clinical purposes should the weighting factor finally need minor revision upward or downward.

The availability of the composite Atherogenic Index value which takes *all* the lipoprotein information into account makes it possible to evaluate the risk of future clinical coronary heart disease with complete lipoprotein *information for each case rather* than with just the S_f0-12 lipoprotein levels as was developed for illustrative purposes earlier in this chapter. The procedure for such risk evaluation is precisely that which was employed with

TABLE XII

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (40-49 YEAR OLD MEN)

(Uncorrected for association of Diastolic Blood Pressure with Atherogenic Index Values)

Atherogenic Index (*units*)	*Relative Risk of Myocardial Infarction* (*setting risk = 1 00 at 30 A.I. units*)
30	1 00
35	1 06
40	1 13
45	1 20
50	1.33
55	1.60
60	2 13
65	2.66
70	3 40
75	4.53
80	6.20
85	8.06
90	10 1
95	12 7
100	15 6
105	19 0
110	23 2

THE RISK OF CORONARY HEART DISEASE ARISING FROM DIASTOLIC BLOOD PRESSURE

In the immediately preceding discussion the problem of calculating the risk of clinical coronary heart disease by measurement of the Atherogenic Index alone has been elaborated. These calculations are correct of and by themselves. If this were all that could be done with the prediction problem, it would represent a great step ahead of no knowledge at all However in Chapter IV it was demonstrated that the blood pressure is a factor independent of the lipoprotein levels in determining the risk of clinical coronary heart disease Therefore it should be possible to improve the segregation of individuals with respect to their risk of future clinical coronary heart disease by taking into

TABLE XI

DISTRIBUTION OF 113 MYOCARDIAL INFARCTION CASES INTO THOSE RANGES OF ATHEROGENIC INDEX VALUES WHICH SEGREGATE THE HEALTHY POPULATION INTO GROUPS EACH CONTAINING 10% OF TOTAL GROUP

Atherogenic Index Ranges for Each Category (Units)	*Number of Myocardial Infarction Cases in each Atherogenic Index Range*
48 and below	2
49-55	2
56-61	3
62-67	4
68-73	5
74-78	7
79-87	11
88-96	18
97-108	25
109 and above	36
Total Number of Cases	113

long in advance of occurrence of clinical coronary heart disease the prediction of relative risk based upon the Atherogenic Index is valid. Precisely the same considerations hold for the Atherogenic Index as held for the lipoprotein measurements out of which it is derived since it is simply a composite measure expressing the information contained in the lipoprotein measurements. In the previous discussion (Chapter III) it was shown that the lipoprotein elevation occurs in advance of clinical coronary heart disease by at least one to three years. It was indicated further, from the study of population trends and the study of individuals, that persons with high lipoprotein values, and hence high Atherogenic Index values, remain high whereas those who are low remain low during most of adult life. Therefore the period of one to three years of predictive value may in all likelihood be extended to 5, 10, 15 or even 20 years before the occurrence of clinical heart disease.

values is directly a measure of *risk* of myocardial infarction for that particular blood pressure range. These data then can be used to construct a table of risk, in terms of the number of infarction cases per 1000 persons at risk at successive blood pressure values. By setting this risk equal to 1.0 at some arbitrary diastolic pressure value, e.g., 50 mm Hg, the risks for all other blood pressure values can be expressed *relative* to the risk at 50 mm Hg. This set of relative risks of myocardial infarction for various diastolic blood pressure values is presented in Table XIII. Thus, wholly independent of any of the lipoprotein information, the relative risk of clinical coronary heart disease has been calculated for various diastolic blood pressure values. If the lipoprotein levels were wholly unrelated to blood pressures the calculation of the risk due to elevation of blood pressure could be immediately superimposed upon the risk due to the blood lipoproteins. However, there is a weak correlation of Atherogenic Index values with blood pressure levels, meaning that in the population-at-large as the Atherogenic Index rises there is anticipated a slight rise in average blood pressure levels and conversely as the diastolic blood pressure rises, there is anticipated a slight rise in the average Atherogenic Index value. Therefore, a small part of the increased risk of clinical coronary heart disease at a particular elevated Atherogenic Index value is the result of the increased blood pressure which, on the average, is associated with that elevation in Atherogenic Index value. Since this rise in blood pressure level with Atherogenic Index is known, the table of risk versus Atherogenic Index can be corrected for the risk rise occasioned by the average rise in blood pressure which accompanies the rise in Atherogenic Index. In Table XIV (a) is presented the risk versus Atherogenic Index data, corrected for the association of blood pressure with Atherogenic Index.

The rise in average Atherogenic Index value with rise in diastolic blood pressure value in the population-at-large is also significant, especially at blood pressures above 70 mm Hg. For diastolic blood pressures below 70 mm Hg, there is almost no detectable change of average Atherogenic Index value with change in blood pressure. Above 70 mm Hg, there is approxi-

account the blood pressure levels as well as the Atherogenic Index values. How is this to be done? In precisely the same fashion as was done for the Atherogenic Index, a population sample of 10,000 men can be divided into 10 sub-segments each containing 1000 men ranked upon diastolic blood pressure values. It is known from data such as those of Yater and co-workers what the distribution of diastolic blood pressure values would be for a group of myocardial infarction cases that would arise out of such a base population of 10,000 men. Therefore the number of myocardial infarction cases for each blood pressure range containing 1000 of the men of the original base population is available from the Yater data. The number of myocardial infarction cases per 1000 men for each range of diastolic blood pressure

TABLE XIII

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION AT VARIOUS DIASTOLIC BLOOD PRESSURE VALUES (MALES)

(Uncorrected for association of Atherogenic Index values with Diastolic Blood Pressure)

Diastolic Blood Pressure mm Hg	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 50 mm Hg)*
50	1.00
55	1.11
60	1.28
65	1.72
70	2.89
75	5.11
80	7.33
85	9.66
90	12.4
95	15.7
100	19.2
105	22.5
110	26.2
115	30.2
120	34.6
130	39.1
140	41.6
150	50.2

But since the relationship of Atherogenic Index with relative risk of myocardial infarction is available (Table XII) it is readily possible to correct the blood pressure risks for the rise in Atherogenic Index with rise in blood pressure. This is illustrated as follows: At a blood pressure of 50 mm Hg the average Atherogenic Index value for 30-39 year old men is 66.0 units, whereas for a blood pressure of 90 mm of Hg, the average Atherogenic Index is 70.6 units. Such a rise in Atherogenic Index itself raises the risk of myocardial infarction. From Table XII this relative risk for 70.6 A.I. units is approximately 1.24 times that

TABLE XIV(b)

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION AT VARIOUS DIASTOLIC BLOOD PRESSURE VALUES (MALES)

*(Corrected for association of Atherogenic Index values with Diastolic Blood Pressure)**

Diastolic Blood Pressure mm Hg	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 50 mm Hg)*
50	1.00
55	1.02
60	1.09
65	1.32
70	2.01
75	3.23
80	4.16
85	4.98
90	5.79
95	6.68
100	7.53
105	8.06
110	8.70
115	9.32
120	9.82
130	10.8
140	11.7
150	12.5

*Each value in this table [illegible]
association [illegible]
data of Tab[illegible]
was made b[illegible]

mately a 2.4 unit rise in Atherogenic Index for a 10 mm Hg rise in diastolic pressure. When the relative risk of myocardial infarction versus diastolic pressure is estimated directly from blood pressure distributions for persons in health and for the myocardial infarction cases that grow out of a healthy population, *part* of the increased risk with increased blood pressure is really the result of the rise in Atherogenic Index with rise in pressure.

TABLE XIV (a)

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (40-49 YEAR OLD MEN)

*(Corrected for Association of Diastolic Blood Pressure with Atherogenic Index Values)**

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30 A.I units)*
30	1.00
35	1 05
40	1.10
45	1 15
50	1.27
55	1.48
60	1.92
65	2 35
70	2 93
75	3 84
80	5 17
85	6 61
90	8.15
95	9 92
100	11 7
105	14 1
110	16 8
115	19 8
120	23.1
125	26 7
130	30 6

* [illegible] Table XII for the [illegible] value utilizing the [illegible] omplete correction, [illegible]

from the blood pressure. Such combination is readily possible if one approximation is made, an approximation that is almost certain to be an excellent one. This approximation is that if a particular elevation in Atherogenic Index value multiplies the coronary disease risk by a certain factor for persons all of whom have one particular blood pressure value, it multiplies the risk by the same factor for persons all of whom have some other blood pressure value. An illustration of this approximation follows: Our previous calculations indicate that the risk of future coronary disease doubles for an increase in Atherogenic Index value from 50 units to 65 units in 40-49 year old men (see Table XII). The approximation being made is that this would hold true if two men were being compared both of whom had diastolic blood pressures of 70 mm Hg, or if both of whom had some other diastolic pressure such as 80 mm, 90 mm or 100 mm Hg. The analogous approximation is made that if a particular elevation in diastolic blood pressure multiplies the coronary disease risk a certain amount for persons all of whom have one particular Atherogenic Index value, it multiplies the risk by the same factor for persons all of whom have some other Atherogenic Index value If either of these approximations deviates from actuality at all, it is extremely doubtful that any such deviation will be appreciable relative to the risk factors that will apply in the comparison of various persons

The combination of the future coronary heart disease risk from blood pressure measurement with that from Atherogenic Index values now becomes simplified Let us set the relative risk for the 45 year-old man who is characterized by an Atherogenic Index value of 30 units and a diastolic blood pressure value of 50 mm Hg at 1 0 (On a *relative* scale the risk of a person can be arbitrarily set at 1 0 for some convenient set of Atherogenic Index and diastolic pressure values) Now, if a 45 year old man whose Atherogenic Index is 85 units and whose diastolic blood pressure is 75 mm Hg is considered, how does he rate compared with the first man with an Atherogenic Index of 30 units and a diastolic pressure of 50 mm Hg? From Table XIV (a) the corrected relative risk in passing *from an* Atherogenic Index value of 30 units to 85 units is 6 61 times as high. Now since this is the

for 66.0 A.I. units. Therefore, an excellent correction of the relative risk of myocardial infarction for a blood pressure of 90 mm Hg versus that for a blood pressure of 50 mm Hg is achieved by multiplying that relative risk by 1/1.24, or 0.81. When this is done, the relative risk for the two pressures no longer has within it that increment in risk due to the Atherogenic Index elevation which goes with the blood pressure elevation. In Table XIII the relative risk for a blood pressure of 90 mm Hg is listed as 12.4 times that for a blood pressure of 50 mm Hg. Multiplying 12.4 by 0.81 yields 10.0, which is the relative risk for a blood pressure of 90 mm Hg compared with that for 50 mm Hg *after removal* of the increase in relative risk which results from the association of Atherogenic Index values with blood pressure levels. The relative risk of myocardial infarction for every diastolic blood pressure value can be corrected in an entirely analogous manner. In Table XIV (b) are presented the risk versus diastolic pressure values corrected for the effect of the association of rising average Atherogenic Index with rising blood pressure. Therefore, these corrected risks of myocardial infarction for each blood pressure value are free of the effects of Atherogenic Index alteration. It is this corrected table of relative risks associated with various blood pressure values that must be used in all subsequent calculation of *overall* risk of myocardial infarction.

COMBINATION OF ESTIMATES OF RISK OF MYOCARDIAL INFARCTION TO OBTAIN OVERALL RISK

Medical interest centers about the *overall ranking* of apparently healthy individuals with respect to the chance, or risk, of development of future clinical coronary heart disease. Since risk rises with increasing Atherogenic Index values and independently with increasing diastolic blood pressure values, it is evident that the overall risk of a person with elevation *in both these* factors must be higher than that for a person with an equivalent elevation only in *one* of the two factors. It is essential, therefore, that some practical method be developed to combine the risks estimated separately from the Atherogenic Index value and

The *overall risk* is therefore 16.8x7.53 or 126.5 times that of a person with an Atherogenic Index of 30 units and a blood pressure of 50 mm Hg.

Similarly, for Case (*b*):

From Atherogenic Index, the relative risk is 1.10 times that for an Atherogenic Index of 30 units.

From diastolic pressure, the relative risk is 7.53 times that for a diastolic pressure of 50 mm Hg.

The *overall risk* is 1.10x7.53, or 8.28 times that of a person with an Atherogenic Index of 30 units and a blood pressure of 50 mm Hg

For Case (*c*):

From Atherogenic Index, the relative risk is 16.8 times that for an Atherogenic Index of 30 units.

From diastolic pressure, the relative risk is 1.09 times that for a diastolic pressure of 50 mm Hg

The *overall risk* is 16.8x1.09, or 18.3 times that for a person with an Atherogenic Index of 30 units and a blood pressure of 50 mm Hg

For Case (*d*):

From Atherogenic Index, the relative risk is 1.10 times that for an Atherogenic Index of 30 units.

From diastolic pressure, the relative risk is 1.09 times that for a diastolic pressure of 50 mm Hg.

The *overall risk* is 1.10x1.09, or 1.20 times that for a person with an Atherogenic Index of 30 units and a blood pressure of 50 mm Hg

With these calculated risks, any two of these men can now be directly compared with respect to *overall risk* of coronary heart disease. The man with the highest risk (Case (a)) has 126.5 times the risk of the person with an Atherogenic Index of 30 units and a diastolic pressure of 50 mm Hg. The man with the lowest risk (Case (d)) has 1.20 times the risk of a person with an Atherogenic Index of 30 units and a diastolic pressure of 50 mm Hg. The comparison of Case (a) and Case (d) is made by comparing 126.5 with 1.20. Therefore Case (a) has 126.5/1.20, or 105.4 [illegible]

increase in risk for the Atherogenic Index change without change in blood pressure, it is now appropriate to consider the risk rise for the blood pressure increase, holding the Atherogenic Index constant. In Table XIV (b) it is shown that a diastolic blood pressure rise from 50 mm Hg to 75 mm Hg corresponds to a relative risk of 3.23 times. *The overall risk of coronary heart disease is obtained by multiplication of that arising from the Atherogenic Index by that arising from the blood pressure.* Therefore, multiplying 6 61x3.23 one obtains 21.4. Therefore, the net, or overall, risk of this person is 21.4 times that of the person with an Atherogenic Index of 30 units and a blood pressure of 50 mm Hg. Thus to compare the coronary disease risk of any person of this age with that for any other person it is simply necessary to multiply together the separate factors for increase or decrease in risk with the change of Atherogenic Index and the change in blood pressure, respectively. Since relative risk was set at 1.0 for an Atherogenic Index of 30 units and a blood pressure of 50 mm, all persons should have their risks calculated with respect to these reference points, and then after multiplying the Atherogenic Index risk by the blood pressure risk, the overall risk thereby obtained may be compared directly for the individuals concerned. This procedure is illustrated below, with consideration of four types of cases:

Case (a) A man 45 years of age with a high diastolic blood pressure (100 mm Hg) and a high Atherogenic Index value (110 units)

Case (b) A man 45 years of age with a high diastolic pressure (100 mm Hg) and a low Atherogenic Index value (40 units)

Case (c) A man 45 years of age with a low diastolic pressure (60 mm Hg) *and a high Atherogenic Index (110 units).*

Case (d) A man 45 years of age with a low diastolic pressure (60 mm Hg) and a low Atherogenic Index value (40 units)

For Case (a):

From Table XIV (a) the relative coronary disease risk (for Atherogenic Index) is 16.8 times that of a person with an Athero genic Index *of 30 units.*

From Table XIV (b), the relative coronary disease risk (for blood pressure alone) is 7.53 times that for a person with a diastolic pressure *of 50 mm.*

cases with Case (d); they can be directly compared. Thus Case (b) has 8.28/18.3 = 0.45 times the risk of Case (c). This last intercomparison illustrates how the effect of a high Atherogenic Index can be offset by the effect of a low diastolic blood pressure, and vice versa. *Overall risk evaluation demands consideration of both Atherogenic Index and blood pressure.*

The illustrative examples above of calculation of overall risk of coronary heart disease were for the intercomparison of 40-49 year old men. Similar calculations are, of course, of interest to the clinician for the intercomparison of 30-39 year old men with each other, of 50-59 year old men with each other, and of 60-69

TABLE XVI

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (50-59 YEAR OLD MEN)

(Corrected for Association of Diastolic Blood Pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30 A.I. units)*
30	1.00
35	1.02
40	1.05
45	1.15
50	1.22
55	1.32
60	1.58
65	1.99
70	2.59
75	3.25
80	4.17
85	5.02
90	5.94
95	6.81
100	7.74
105	8.81
110	10.0
115	11.2
120	12.8
125	14.3
130	16.0

(d). This, it is seen, is a relatively enormous segregation of these two cases upon coronary heart disease risk, based upon the two measurements, Atherogenic Index and blood pressure. Cases (b) and (c) have intermediary values of the *overall risk*, Case (b) having a risk of 8.28/1.20, or 6.9 times that of Case (d), and Case (c) having a risk of 18.3/1.20 or 15.3 times that of Case (d). It is of course not necessary to compare all the other

TABLE XV

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (30-39 YEAR OLD MEN)

(Corrected for association of diastolic blood pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30)*
30	1.00
35	1.24
40	1.46
45	1.68
50	1.90
55	2.20
60	2.59
65	3.10
70	3.78
75	4.97
80	6.46
85	8.20
90	10.2
95	12.0
100	13.8
105	16.0
110	18.8
115	22.2
120	26.3
125	30.4
130	35.3
135	40.1
140	45.0
145	50.6
150	55.6

cases with Case (d); they can be directly compared. Thus Case (b) has 8.28/18.3 = 0.45 times the risk of Case (c). This last intercomparison illustrates how the effect of a high Atherogenic Index can be offset by the effect of a low diastolic blood pressure, and vice versa. *Overall risk* evaluation demands consideration of both Atherogenic Index and blood pressure.

The illustrative examples above of calculation of overall risk of coronary heart disease were for the intercomparison of 40-49 year old men. Similar calculations are, of course, of interest to the clinician for the intercomparison of 30-39 year old men with each other, of 50-59 year old men with each other, and of 60-69

TABLE XVI

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (50-59 YEAR OLD MEN)

(Corrected for Association of Diastolic Blood Pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30 A I units)*
30	1.00
35	1.02
40	1.05
45	1.15
50	1.22
55	1.32
60	1.58
65	1.99
70	2.59
75	3.25
80	4.17
85	5.02
90	5.91
95	6.84
100	7.74
105	8.81
110	10.0
115	11.2
120	12.8
125	14.3
130	16.0

(d). This, it is seen, is a relatively enormous segregation of these two cases upon coronary heart disease risk, based upon the two measurements, Atherogenic Index and blood pressure. Cases (b) and (c) have intermediary values of the *overall risk*, Case (b) having a risk of 8.28/1.20, or 6.9 times that of Case (d), and Case (c) having a risk of 18.3/1.20 or 15.3 times that of Case (d). It is of course not necessary to compare all the other

TABLE XV

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (30-39 YEAR OLD MEN)

(Corrected for association of diastolic blood pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30)*
30	1.00
35	1.24
40	1.46
45	1.68
50	1.90
55	2.20
60	2.59
65	3.10
70	3.78
75	4.97
80	6.46
85	8.20
90	10.2
95	12.0
100	13.8
105	16.0
110	18.8
115	22.2
120	26.3
125	30.4
130	35.3
135	40.1
140	45.0
145	50.6
150	53.6

genic Index data. These tables are to be used for calculations of relative risk within each age decade just as in the illustrative examples above for 40-49 year old men.

THE PROBLEM OF AGE IN THE PREDICTION OF FUTURE CLINICAL CORONARY HEART DISEASE

Since all the development of overall risk estimates of future coronary heart disease was carried through holding age bracket constant, such risk estimates are appropriate to compare a particular man of *one* age, e.g., 44 years, with another man also 44 years of age. Stretching the estimates one can without appreciable error compare two men in the same age decade, e.g., 40-49 years, even though they differ in age by a couple of years. However, it would *not* be appropriate to use such risk tables directly to compare a 35 year old man with a 65 year old man. Nor would it be permissible to use these tables directly to compare a 40 year old woman with a 40 year old man, since the tables were developed with data derived from measurements on men. But every clinician wants to be able to make precisely such comparisons, since he is interested in how two people rate in terms of risk of myocardial infarction whatever may be their age and whether or not both are of the same sex The problem of transferring the predictive tables to the female sex will be dealt with in extenso in Chapter VIII The problem of intercomparisons between men of widely separated ages is best handled by bringing in evaluation of absolute risks of coronary heart disease in addition to relative risks

ABSOLUTE RISK OF CORONARY HEART DISEASE VERSUS RELATIVE RISK

Relative risk estimates for any two individuals describe whether one of them is two, four, ten, or more times as likely to develop clinical coronary heart disease in a particular time interval as is the other. As stated above, such risks have been evaluated for the case where both individuals are of the same, or nearly the same, age However, if the risk estimates were converted to an *absolute* basis instead of the relative basis, there

year old men with each other. Since for each age decade under consideration a table of risk versus Atherogenic Index and risk versus diastolic blood pressure is needed, such tables must be provided. The table of risk versus diastolic blood pressure, which is based upon the magnitude of the difference in blood pressure for Yater's series of cases of coronary heart disease will be used for all the age groups, since no better data are available for each specific age group. It is doubtful that there would be significant alterations in the relative risk due to blood pressure if separate tables were available for each age group. However, specific data are available from which tables of risk versus Atherogenic Index can be separately constructed for each additional age decade, namely 30-39 years, 50-59 years, and 60-69 years. Tables XV, XVI, and XVII provide these relative risk versus Athero-

TABLE XVII

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (60-69 YEAR OLD MEN)

(Corrected for Association of Diastolic Blood Pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30 A.I. units)*
30	1.00
35	1.02
40	1.05
45	1.15
50	1.41
55	1.74
60	2.34
65	3.19
70	4.31
75	5.42
80	6.50
85	7.70
90	8.95
95	10.2
100	11.4
105	13.0
110	14.6
115	16.5

fore, for the 35 year man with average Atherogenic Index (70.2 units) and average blood pressure (71.0 mm Hg) as it is for the hypothetical reference man with Atherogenic Index of 30 units and diastolic pressure of 50 mm Hg. Now, since the absolute risk, or incidence rate, of fatal coronary disease is 50 per 100,000 per year for the average man, it must be 50 divided by 8.53, or 5 86 per 100,000 per year for the hypothetical reference man at 30 units of Atherogenic Index and 50 mm Hg. Since all of our relative risk calculations described previously are made in terms of the risk compared with the hypothetical reference man, it becomes immediately possible to convert any relative risk calculated into the absolute risk by simply multiplying by the value 5 86 per 100,000 per year. This may be illustrated as follows: Suppose a 35 year old man has an Atherogenic Index of 100 units and a diastolic pressure of 90 mm Hg From Table XV, from Atherogenic Index, his risk relative to the hypothetical reference man (A I. = 30 units) is 13.8 times as high. From Table XIV, from diastolic pressure, his risk relative to the reference *man* (BP = 50 mm Hg) is 5 79 times as high. Multiplying these values together, we obtain 13 8x5 79, or 79 9 times as high for the overall relative risk The conversion to absolute risk is achieved by multiplication of 79 9 by 5 86 This yields an absolute risk of 468 per 100,000 per year for the 35 year old man with an Atherogenic Index of 100 units and a blood pressure of 90 mm Hg This value of absolute risk is directly comparable with similarly calculated absolute risks for men *at any age*. *It is*, therefore, evident that having the absolute risk for the hypothetical reference man (A I = 30 units, BP = 50 mm Hg) at each age is highly useful for the purpose of converting relative risks into absolute risks It was demonstrated above how this absolute risk is obtained for the hypothetical reference *man* of 35 years of age using the combination of the relative risk tables plus the U. S. Vital Statistics to provide the risk for the person with average Atherogenic Index and average blood pressure. Such absolute risks for the hypothetical reference man for each decade have been calculated and are reproduced as follows:

would exist no problem whatever to compare the risk for a 35 year old man with that for a 65 year old man or a man of any age. *Absolute* risks are expressed in terms of the number of men developing clinical coronary heart disease per 100,000 persons exposed in a specific time period, e.g. one year. Thus if a certain 35 year old man belongs to a group where 10 out of 100,000 will develop clinical coronary heart disease in one year and a certain 65 year old man belongs to a group where 50 out of 100,000 will develop clinical coronary heart disease in one year, it is obviously possible to compare these *absolute* risks *directly* and to state that this 65 year old man has five times the risk of clinical coronary heart disease as the particular 35 year old man under consideration. How are such absolute risks to be obtained for any two men?

The U. S. Vital Statistics provide the average incidence rate of fatal coronary heart disease for men at various ages (see Chapter VII). Let us consider the use of such information to translate relative risks into absolute risks for any particular individual For 35 year old men in the United States the incidence rate of fatal coronary disease is approximately 50 per 100,000 persons per year. This may be expressed otherwise as the *average risk* of fatal coronary heart disease for 35 year old men. To a first approximation (and one completely adequate for all our purposes here) this risk may be considered to be that which applies to the 35 year old man *who has the average values of the Atherogenic Index and of the diastolic blood pressure.*

For this age, average Atherogenic Index=70.2 units, and average diastolic blood pressure=71 0 mm Hg. The question to ask now is "What is the absolute risk for the hypothetical *reference* man of 35 years of age, with an Atherogenic Index of 30 units and a diastolic pressure of 50 mm Hg?" The first step is to compare this hypothetical reference individual with the average man of 35 years of age From Table XV the relative risk of coronary disease for an Atherogenic Index of 70.2 units is 3.79 times that for an Atherogenic Index of 30 units. From Table XIV the relative risk for a diastolic blood pressure of 71 0 mm Hg is 2.25 times that for a diastolic pressure of 50 mm Hg. The *overall* relative risk for 3.79x2.25, or 8 53 times as high, there-

THE QUESTION OF "FALSE POSITIVE" PREDICTIONS

It is worthwhile contemplating the absolute risk values in connection with the question of so-called "false positive" prediction. Thus, for the illustration above for a 65 year old man with a high Atherogenic Index (100 units) and a blood pressure well above average, namely 90 mm Hg, the absolute risk of fatal coronary disease was calculated to be 8217 per 100,000 persons per year Out of 100,000 such men, 8217 would die in one year of coronary heart disease, *but* 91,783 would survive in that year. Evidently many more people would survive the year than would die of coronary disease. There are those who would ask the question, "Does this not mean that the Atherogenic Index-blood pressure risk calculation has falsely indicated a high risk of fatal coronary heart disease?" The answer is unequivocally and emphatically, "No" Even though more persons will survive *the* year than will die, 8217 deaths per 100,000 is still a very high risk and is in no sense a "false" prediction. The entire point of such risk estimates is the development of an ability to select out of an otherwise homogeneous population sample those persons who carry 2, 5, 10, 20, 100, or 500 times the risk of coronary heart disease death than characterizes other members of the population sample. The issue is *not* selection of some group of *persons, all* of whom or *most* of whom will be dead of coronary disease within any specified short time interval. It can readily be shown that the argument concerning "false positives" readily reduces to a logical absurdity Suppose *that* a risk category were identified where 995 out of 1000 persons would be dead of coronary disease in a one year period In this event those who talk of false positives might say that this is good prediction for a one year period, but they could ask about the validity of the risk estimate for the five-minute period just after the blood pressure was determined and the blood sample was withdrawn from Atherogenic Index determination Even for a group of persons in which 995 out of 1000 *will be dead* in one year, it is true that more than 999 out of 1000 would still be alive after five minutes. Does this mean that this group has been *falsely* predicted to show a high risk of coronary disease? Manifestly, this type of reasoning concerning "false positives" *can* lead to ridiculous conclusions and

Age Decade	*Absolute Risk of Fatal Coronary Disease for the Hypothetical Reference Man at Atherogenic Index = 30 Units and Diastolic Pressure = 50 mm Hg.*
30-39 years	3.86 per 100,000 per year
40-49 years	12.9 per 100,000 per year
50-59 years	56.1 per 100,000 per year
60-69 years	124.5 per 100,000 per year

Illustration of how these absolute risks allow direct comparison of men differing widely in age is now in order. In the *development above it was shown that a 35 year old man whose* Atherogenic Index is 100 units and whose diastolic pressure is 90 mm Hg is 468 per 100,000 per year. How would this compare with the risk of a 65 year old man having the same Atherogenic Index (100 units) and the same diastolic pressure (90 mm Hg)?

For a 65 year old man, from Table XVII, the relative risk for an Atherogenic Index of 100 units is 11.4 times as high as for the reference man with an Atherogenic Index of 30 units. From Table XIV, the relative risk for a diastolic blood pressure of 90 mm Hg is 5.79 times as high as for the reference man with a diastolic pressure of 50 mm Hg. The overall *relative* risk for the 65 year old man with an Atherogenic Index of 100 units and a diastolic pressure of 90 mm Hg is, therefore, 11.4x5.79, or 66.0 times as high as for the hypothetical reference man of 65 years of age with an Atherogenic Index of 30 units and a diastolic blood pressure of 50 mm Hg. But this hypothetical reference man has an *absolute* risk of fatal coronary heart disease of 124.5 per 100,000 per year Therefore the 65 year old man with an Atherogenic Index of 100 units and a diastolic pressure of 90 mm Hg has an absolute risk of 66.0x124.5, *or* 8217 *per* 100,000 *per year*. The comparison of this 65 year old man with the 35 year old man having the *same* Atherogenic Index and the same blood pressure *is made by dividing 8217 by 468. Therefore the 65 year* old man has 17.6 times as high a risk of coronary heart disease as does a 35 year old man, even though both have the same Atherogenic Index and the same blood pressure. The procedure for comparing any two other men at any ages, Atherogenic Indices, and blood pressures would be identical to that just developed.

THE INFLUENCE OF VARIABILITY OF THE ATHEROGENIC INDEX AND BLOOD PRESSURE MEASUREMENTS ON PREDICTIVE POWER

It is of course true that with respect to any biochemical measurement, such as Atherogenic Index value, or any physiological measurement, such as blood pressure, there is a certain degree of fluctuation observed if the measurement is made repeatedly on the same person. This fluctuation in measurement originates from at least two major sources. The first is what may be regarded as biological variation, namely, the fact that a human does not show absolutely constant values of very many biochemical or physiologic variables over a period of time. The second major source of variation is that due to technical error of measurement. What we see in the overall when a given variable is measured, such as the Atherogenic Index or the blood pressure, is the combined effect of biological variation and technical error in measurement As a result of the operation of these two factors a person will not show exactly the same Atherogenic Index value or blood pressure value determined on two separate occasions either a day, week, month, or year apart. It is true that such variation would tend to move the position of a person somewhat on a scale of risk of future coronary disease This hardly need interfere with the enormous usefulness of the predictive measurement First of all, variation of the Atherogenic Index is in general small, although it definitely exists. Hence a person who is in the highest quarter of the population will, in the main, remain in the highest quarter of the population, whereas a person in the lowest quarter of the population with respect to the Atherogenic Index will, in the main, remain in the lowest quarter The precise extent to which Atherogenic Index measurements vary for individuals over a period of one to three years is now known Studies are available for 213 consecutive men between the ages of 20 and 59 years of age upon whom Atherogenic Index measurements were made on one periodic employment examination and on a second examination one to three years later. (Exclusion of the effect of major dietary alterations was achieved by elimination from this series of any men who had gained or lost five or more pounds in weight over the time inter-

away from any constructive approach to the coronary heart disease problem.

It is always pertinent, when confronted with such problems, to review the nature of the objectives toward which one is working. In the prediction of risk of future clinical coronary heart disease, the objective is *utilization* of the information obtained to take constructive steps toward *prevention* of that disease. It would be remarkable indeed if there were a method available to determine that a particular individual is *the* one who will have a myocardial infarction in 30 days If this were possible, every effort could be made to apply preventive measures for this particular individual. Such prediction is simply not possible now nor does it appear that it will be possible in the near future. But the methods described in this chapter do permit identifying individuals with five, ten, or more times the risk of development of clinical coronary heart disease in comparison with average individuals. Can such information be utilized to achieve our objective? Let us suppose that a particular individual has been demonstrated to show *twice* the average risk of development of coronary heart disease during a one year period. Suppose further that such risk can be reduced in half by medical measures If every person whose risk is twice or more than twice average had his or her risk cut in half by medical measures, the net result of such a program would be a lowering of mortality due to coronary heart disease approximately by a factor of two. This would obviously be considered as a major medical triumph. The type of risk estimates developed here allow for progress toward precisely such a goal Great progress can definitely be made in this direction even though it is not possible to predict the date and hour that a specific individual will experience myocardial infarction or even to predict that he *ever* will. While this approach will lead to advice of prophylactic measures for *some* persons who *might* escape the disease even with a high risk, it would be utter folly to underestimate the real potential and power of this type of preventive medical approach to coronary heart disease.

WHO IS IN NEED OF PREDICTION OF THE RISK OF FUTURE MYOCARDIAL INFARCTION?

From the data and calculations presented up to this point it is clear that a population of individuals otherwise comparable can be divided on the basis of lipoprotein and blood pressure measurement into groups characterized by a very low risk of coronary heart disease in a specified time interval, an intermediary risk in the same time interval, or a very high risk in the same time interval. The question facing the clinician is, "What group of individuals is in need of such predictive information concerning the risk of future coronary heart disease?" Certainly those who have already manifested clinical signs and symptoms of overt coronary heart disease are hardly in need of prediction of whether they are prone to develop coronary heart disease. In the population-at-large no one has ever been able to distinguish by standard medical examinations, including electrocardiography, any group of adults who can be said to be free of the risk of future clinical coronary heart disease The suddenness of occurrence of clinical coronary heart disease in "persons in the best of health" eloquently refutes the possibility of pre-selecting by usual means any part of the population which carries an excessive risk from any part of the population which has little or no risk. This being the case it is quite clear that *every adult* in the population represents, without auxiliary special information, a potential candidate for future clinical coronary heart disease. Therefore, every adult in the population is a candidate for *evaluation* of his risk of future coronary heart disease. To be sure, we know from vital statistics for the country that men of 25 years of age have a lesser risk of coronary heart disease than men of 35 years of age, and correspondingly men of 35 years of age have a lesser risk than do men of 45 years of age, etc With respect to imminence of disease, it might be considerably more pertinent to segregate 45 year old men on the basis of risk of future clinical coronary heart disease than to do so for 25 year old men. However another consideration must temper this view. All the evidence indicates that the clinical aspects of coronary heart disease represent a culmination of the slow accumulation of coronary artery narrowing The major predictors of future clinical coronary disease,

val between the two examinations.) The best approximation of the true Atherogenic Index values for these cases is to take the average of the two measurements for each person. When this is done, it is found that the following holds:

(a) 58% of these men varied fewer than 5 Atherogenic Index units from their average value over the 1-3 year period.

(b) 25% of these men varied between 5 and 10 units from their average value over the 1-3 year period.

(c) 13% of these men varied between 10 and 15 units from their average Atherogenic Index value over the 1-3 year period.

(d) Only 4% of these men varied 15 or more units from their average Atherogenic Index value over the 1-3 year period.

Therefore it is relatively rare for a man to be significantly misclassified on the Atherogenic Index—coronary disease risk scale even with a *single* measurement of the Atherogenic Index value. Multiple measurements over a period of time for an individual will allow placement on the risk scale with great precision.

The blood pressure measurement is somewhat more variable both on a biological and technical basis. However, here again if one is interested in assessing the risk of someone with respect to coronary heart disease (and such risk is probably one of the most important measurements that can be made for an individual in health in the effort to safeguard his future health) one can certainly afford to make repeated blood pressure measurements. Since the blood pressure does tend to vary some, one might want to make a series of measurements spaced at *specific time intervals* to determine the individual's usual, or habitual, blood pressure. Blood pressure measurements taken under relatively standardized conditions should be utilized in coronary disease risk estimates. Thus, if an individual happened to have a single blood pressure value of 100 mm Hg under a single special circumstance, whereas most of the time he is at 80 millimeters of mercury, it would hardly make sense to consider 100 mm Hg as the pressure value to use in assessing coronary disease risk

measure with recent poliomyelitis immunization of adults and, at least for military personnel and travelers, innoculation for several other diseases. However, the idea that vascular disease may enter this realm of preventive medicine is one which will meet with some skepticism and lack of understanding in certain quarters. Yet all the evidence points in this direction. There will undoubtedly be those who say the idea of considering every adult as a patient or a potential patient with respect to a disease like coronary heart disease would mean a fabulous task for the medical profession. It will be a fabulous task for the medical profession, but one abundantly justified by the fabulous importance of the problem that lies before it in this field. Further, there will be some who will ask whether we might not dispense with individualization in prediction of heart disease risk through identification of those with lipoprotein metabolic errors and/or blood pressure elevation, and instead develop a preventive hygiene that can be advised for the population-at-large broadly without the necessity for individual attention. Preventive hygiene measures on a broad basis are highly desirable where feasible. For example, if it were discovered that a particular atmospheric pollutant resulting from industrialization of our cities were the cause of a particular disease, certainly the best measure for minimization of the hazard due to this pollutant would be a concerted attempt to rid the atmosphere of it. This would represent broad-scale application of a generalized hygiene. Similarly, if it could be shown that a specific dietary element were injurious to a large number of individuals or to all, one could recommend a generalized hygiene to eliminate this particular noxious agent from the dietary environment. There is every reason to make progress in this direction of generalizing our efforts toward a preventive hygiene for coronary heart disease. However, as the evidence develops in this area, it appears more and more that *individualization* will be needed, and needed *over and above any such generalized measures*. Thus, it is now known that in certain individuals the S_f0-20 lipoprotein elevation is the primary reason for an increased risk of future clinical coronary heart disease. In other individuals the S_f20-400 lipoprotein elevation is the primary reason for an increased risk of future coronary heart dis-

namely the lipoprotein levels and the blood pressure, appear to derive their relationship with clinical coronary heart disease via their relationship with coronary arteriosclerotic narrowing. Therefore, if a preventive regimen is to be devised for persons with high risks, the prediction of risk should be accomplished as early as feasible, in order to inhibit the slowly developing coronary artery narrowing, and the corresponding accumulation of risk of ultimate clinical coronary heart disease. This means that the earlier it is possible to use predictive information, the more favorable the outlook for accomplishments in minimization of the risk of ultimate development of overt coronary heart disease. By the time a man is in his twenties his lipoprotein levels can certainly provide a great deal of information concerning the risk of later clinical coronary heart disease. This is the appropriate time to start evaluation of risk. Further, since there is no way of excluding *anyone* in the population as a potential bearer of a high risk of future coronary heart disease, the need for screening the future risk of coronary heart disease extends over the entire population of adults of any country This is undoubtedly a rather radical concept to some. However, some reflection on the problem will readily reveal that unless and until this concept is understood and utilized broadly by the medical profession, the real hope of inhibiting coronary heart disease and cutting down its enormous morbidity and mortality can hardly be realized. This means an entirely new concept for the physician interested in vascular disease as to who is a "patient." We have, in adult medicine, for so long been oriented toward the therapeutic side of medicine, treating diseases once they have become clinically manifest, that it will undoubtedly be difficult, both from the point of view of the physician and of the potential patient, to alter this concept Yet the concept of preventive medicine has taken hold and is taking hold in new areas every day In pediatric practice, for example, the idea of minimizing the risk of such entities as pertussis, typhoid fever, tetanus, diphtheria, poliomyelitis, and other diseases is well established, and immunization of most children is routine. Every child is regarded as a potential candidate for these diseases and hence is deserving of preventive medicine. In the adult field this has been extended to some

many industries have for several years been in the habit of having annual preventive medical check-ups. Such preventive medical check-ups are gradually coming to include additional features of examination, laboratory and clinical, which may discover predisposition to certain diseases at a time when preventive efforts may be really effective. This concept of preventive hygiene is not new, but simply one that requires extremely broad expansion to include thousands of times the numbers of individuals who are now covered by it But progress of this sort, considering the educational aspects involved, may take many years to achieve. It would be naive to believe that simply stating the problem to the physician population and through that group to the public-at-large would see overnight the accomplishment of the desired end It is very important to attempt to lower the time gap between *application* of what we have available to us in our armamentarium of prevention of disease and its actual use to as few years as possible During such an interim time period a great deal can be accomplished by broadening the use of predictive methods for determining the risk of coronary disease to include at least those people who carry the most excessive risk of early coronary heart disease.

As an illustration of this approach, some glaring examples of such groups with very high potential coronary disease risk deserve consideration There exist perhaps as many as one percent of the individuals in the population of the United States who come from families characterized by a marked heritable tendency to have abnormally high levels of lipoproteins of one class or another. In such families overt xanthomata are common, xanthoma tuberosum, xanthoma planum of the hands, xanthoma tendinosum, or xanthelasmata about the eyelids. In these families not all individuals are afflicted with the abnormally high lipoprotein levels, but many are. Unless the members of such families are already characterized by manifest *xanthomatosis*, they go unrecognized and nothing is done for them Some with overt xanthomatosis who have not yet developed overt cardiovascular disease are discovered by physicians because the patients are concerned over the cosmetic aspects of their lesions

ease. In this latter group, the S_f0-20 lipoproteins may be moderate or even very low in level. In still other individuals it is an elevation of all the lipoprotein classes in this general region from S_f0-400 that accounts for the risk of future coronary heart disease. And added to each of these possibilities, there is the factor of elevation of blood pressure together with one or another type of lipoprotein elevation that creates a high risk of future coronary heart disease. *The metabolic factors which control the level of the* S_f0-20 lipoproteins are not in general the same as those that control the level of the S_f20-400 lipoproteins. This is already evident from the fact that individuals can be high in one class of lipoproteins but low in another. It appears highly unlikely that the future will readily see a dietary approach or a pharmaceutical approach that will at once correct *all* the different types of metabolic aberrations that lead to lipoprotein elevation. Therefore individualized attention appears inevitable Indeed a regimen that might favorably affect one lipoprotein class can be very unfavorable for another class. Were sights focussed on the correction of just one of the lipoprotein classes involved without proper attention to the others in a mass generalization of a dietary or pharmacologic preventive hygiene, a great deal of harm might accrue to certain individuals. Such a result could hardly be called an aim of preventive medicine or of medicine in general. Thus, the existence of several types of defects that can lead to an increased risk of clinical coronary heart disease and the unlikely prospect that any simple specific preventive measure will work for everyone on a "blind" basis means that individualization of preventive medical efforts appears essential. The facilities for measurement of the status of every adult individual with respect to lipoprotein level on a schedule such as every one to three years beyond the age of 25 years have long been available. The problem will, first, be largely one of having the physician population recognize the need for such a preventive approach to the problem of coronary heart disease. The public will then need to be educated by the physician concerning the vital role of *preventive* medicine with respect to coronary heart disease Already, many individuals under the advice of their own competent physicians and the executives of

excessive rates. Such persons are, therefore, in need of preventive measures to avert the same type of clinical occurrence as that experienced by the index case. Certainly for anyone with overt coronary heart disease below the age of 40 years, a lipoprotein analysis in all blood relatives is urgent. With less force the same would hold true for the families of persons developing overt coronary heart disease between 40 and 50 years of age. Another stigma that is common in the population and which is at times associated with a lipoprotein disorder on a heredofamilial basis is arcus senilis. The presence of a well-marked arcus senilis in a relatively young person, for example, under 40 years of age, distinctly suggests the individual deserves an early lipoprotein analysis. A surprisingly high frequency of elevation of the S_f0-12 or S_f0-20 lipoproteins will be found in such cases.

Diabetes mellitus will be considered *in extenso* in Chapter XII However at this time it can be emphasized that what excessive risk of coronary heart disease does exist for persons with diabetes mellitus arises largely, if not completely, from elevation of lipoprotein levels or elevation of blood pressure, or both. The lipoprotein and blood pressure status of every diabetic patient deserves early determination, both from the prognostic and management aspects of that person's disease There is no longer any reason for the blanket generalization to the diabetic patient that he carries a hazard of premature coronary heart disease simply because he is diabetic. Such risk can now be determined precisely If the particular diabetic patient should be one of the many fortunate diabetics who do not show the elevation in lipoproteins or the elevation in blood pressure which would accompany an excessive risk of coronary heart disease, he could be vigorously re-assured concerning his outlook by his medical advisor Thus, even though there may be a period of time before the population-at-large is evaluated with respect to lipoprotein and blood pressure status, every diabetic deserves an early evaluation Still another group that deserves consideration comprises those individuals who at one time or another have been treated for thyroid disease A large majority of these may have been treated for a previous hyperthyroidism and some, for goiter without hyperthyroidism. Many of these individuals are

tion is the major feature of therapy. Yet it is well-known that the individuals in such families who are characterized by extremely high lipoprotein levels are prime candidates for very early coronary heart disease and for other related entities such as peripheral vascular disease and cerebral vascular disease. The rate at which the ranks of such families are decreased by premature deaths from coronary heart disease and its related entities is truly appalling, with a large proportion of deaths occurring below forty years of age. For those persons who manifest xanthomatosis there is not a great deal of difficulty in clinical diagnosis of the existence of the xanthomatosis, but all too often nothing is clinically done for the members of these families without the overt lesions For example, in a family where any individual has xanthoma tendinosum with its attendant massive S_f0-12 or S_f0-20 lipoprotein elevation, there exists the high likelihood that brothers, sisters, other relatives, and offspring, even below the age of 5 years, may already have the same massive lipoprotein defect as the index case. These individuals, not yet having developed skin lesions or tendon lesions, are unaware of the tremendous hazard of coronary heart disease they may have inherited and nothing is generally done to attempt to reduce this hazard In such families *every* blood relative of individuals known to be characterized by xanthomatosis of any form requires urgent evaluation of the lipoprotein status as a first step toward broader application of the principle of preventive medicine in coronary heart disease.

Other familial situations would deserve early consideration of an evaluation of the lipoprotein and blood pressure status for members of the family It is the rule to find that young individuals who develop clinical coronary heart disease show *extremely* elevated lipoprotein levels, with this elevation frequently being heredo-familial in origin Siblings of such individuals, parents and children may well be found to be afflicted with a similar lipoprotein disorder. Hence, when coronary disease occurs at an early age in a person, it is very pertinent to examine the lipoprotein status of every blood relative who is available in the effort to discover other members of the family in whom the coronary heart disease risk may be building up at

Chapter VI

THE FAMILIAL ASPECTS OF CORONARY HEART DISEASE

ONE OF the most widespread impressions in medicine concerning coronary heart disease is that it occurs prematurely in certain families. Some cardiologists have crystallized this impression with statements to the effect that perhaps one of the best ways to avoid clinical coronary heart disease is to choose one's ancestors wisely The widespread character of this concept implies that there must be some evidence to support it, and indeed there does exist a certain amount of evidence. However, it can be stated at the outset that the relationship between familial factors and coronary heart disease is far from a perfect one. Therefore, any broad *generalization* based upon a statement that a family history of longevity can be relied upon to protect against coronary heart disease, or that a very poor family history insures that coronary disease will occur in a given individual will be very far from the truth

The real question of interest is whether or not familial factors operate in coronary heart disease in the population-at-large, out of which is drawn the vast bulk of our patients with early clinical coronary heart disease In certain special types of families the hereditary, or heredo-familial, aspect of clinical coronary heart disease is unquestioned, since a very solid body of evidence has implicated a familial factor in these special groups predisposing to the occurrence of coronary disease. This is true of those families in which a hyperlipoproteinemia of some variety is present Earlier, such families had been described in terms of elevation of the serum cholesterol level or the blood total lipid level, but now such entities can be more precisely defined and delineated in terms of the particular spectrum of lipoproteins

followed for a short period of time in the medical center or in the office in which they were originally diagnosed and treated. Thyroid replacement therapy has been provided for many such patients who were left with a mild residual hypothroidism. Yet it is very common for the individual himself to assume that such replacement therapy is temporary and eventually he may stop taking thyroid substance and may remain for years in a hypothyroid state. Such individuals may not feel seriously ill or have sufficient special complaints referable to their thyroid status to seek medical care. If they have been affected by thyroid deficiency to the extent that they acquire the marked elevation of S_f0-20 lipoproteins which characterizes thyroid deficiency (see Chapter XIII), they may be carrying a markedly excessive risk of future clinical coronary heart disease. Therefore, any individual who has, for whatever reason, at one time had a thyroidectomy or a treatment of thyroid disease by destructive agents such as x-ray or radioactive iodine certainly deserves a periodic evaluation of the lipoprotein status to determine whether there is any need for replacement therapy with thyroid substance or one of its congeners.

As one considers the several possibilities, familial lipoprotein derangements, thyroid disorders, diabetes mellitus, families of individuals with early coronary disease, and others, it becomes apparent that the groups in need of early evaluation of their status with respect to risk of coronary disease constitute large numbers of persons. These groups certainly represent the basis for a minimum effort that the medical profession should make in a start toward a significant preventive medicine with respect to coronary heart disease Ultimately this effort must extend to everyone in the population-at-large

elevation. Xanthoma tuberosum is common in these families. Coronary heart disease at an early age is also rampant in this particular heredo familial disorder. Again, there appears to exist no evidence that, at the same degree of elevation of lipoprotein level, there would be any difference in the prognosis with respect to early coronary heart disease in the presence or absence of xanthomatosis. A third group of individuals showing a heredo-familial disorder of lipoprotein levels is that known as the "essential hyperlipemia" group This group of individuals is characterized in general by the absence of xanthomatous lesions These families are discovered when a member of the family is incidentally found to show markedly creamy serum in the fasting state They are characterized by massive elevation in lipoproteins from s_f20 to s_f100, and in most cases, additional massive elevation of lipoprotein levels of those from s_f100 all the way to chylomicrons It is the presence of the very large lipoproteins in high concentration that accounts wholly for the extreme turbidity of the serum in such cases. Characteristically, the s_f0-12 lipoprotein levels are low in such cases, and the s_f12-20 lipoprotein levels are usually not different from those in the population-at-large For some reason there is an erroneous concept in the literature that such individuals seem to be free of the risk of coronary heart disease. This concept is distinctly incorrect, for when such persons have the elevation of s_f20-400 lipoproteins, they carry the high risk of coronary heart disease associated with such an elevation. Most likely the reason for the good prognosis previously assigned to these individuals is that the handful of cases reported in the literature have in the main been children and very young adults. As a result these individuals have been thought to be free of coronary disease risk in spite of their lipoprotein elevation, when actually the reason why they are free of coronary heart disease is that they have been studied at such a *relatively early age*

Even if all these various heredo-familial lipoprotein disorders are combined, they may still be regarded as a rather special group when compared with the population-at-large. Indeed such groups are considered so special that some workers refer to their disease of the vascular system as xanthomatosis of the vascular

which is abnormal[32]. Families do exist with extreme elevation of one or another lipoprotein class, and in these families it is well documented by evidence reported throughout the world that premature clinical coronary heart disease is rampant. To be sure, *some* of the members of these families escape premature clinical coronary heart disease, but that there is a marked increase in the frequency of such disease in these families cannot be doubted. One such type of family is that characterized by massive elevation of the s_f0-12 or s_f0-20 lipoprotein class. In members of these families where the lipoprotein elevation is extreme and where enough time has elapsed, xanthomatosis in the form of xanthelasma (xanthoma of the eyelids), xanthoma tendinosum, and even planar xanthomatosis of the palms is observed There has been some debate in the literature concerning whether or not those members of the family who show the elevation in the blood lipids without the overt xanthomatosis really carry any pre-disposition to coronary heart disease[33]. There is very little question but that the real essence of this problem is that, in order to develop xanthomatosis, the level of lipoproteins has to be quite high and this lipoprotein elevation has to have existed for some period of time. The absence of xanthomatosis in the presence of a high lipoprotein level is quite often traceable to the fact that the individual is relatively young[34]. Given enough time, many of these individuals do develop the xanthomatosis. There exists no reason to expect that the lipoprotein elevation without xanthomatosis carries any different prognosis with respect to early coronary heart disease than does the same degree of lipoprotein elevation with the xanthomatosis, provided of course that any age differential that exists is taken into account. A second type of disorder which is a familial one is that characterized by massive elevation primarily in the S_f12-400 class of lipoproteins, especially the S_f20-400 part of this class of lipoproteins. In such families the lipoprotein derangement is also an inheritable trait with those members of the family who do inherit it showing the same lipoprotein disorder, namely, elevation of the s_f12-400 or s_f20-400 lipoprotein class. It is interesting that, on the average, such individuals show a depression of the s_f0-12 lipoprotein level rather than an

directions. The specific evidence available from such studies deserves critical examination here

DIRECT STUDIES OF THE INCIDENCE OF CARDIOVASCULAR DISEASE IN THE FAMILIES OF INDIVIDUALS WITH OVERT CORONARY HEART DISEASE

One study of the familial patterns in patients with coronary heart disease is that of Gertler and White[36], a part of their overall study of ninety-seven men who had developed clinical coronary heart disease below the age of 40 years. In that study there were 97 men who had developed coronary heart disease below the age of 40 years and 97 matched controls, matched as well as possible by age, sex, and by other variables such as occupation The matched group of controls was overtly healthy and free of any symptoms or signs of clinical coronary heart disease. Interviews conducted in the course of the examination of all these subjects developed data concerning the incidence of cardiovascular disease and deaths due to cardiovascular disease in the mothers, in the fathers, and in the siblings of the 97 men with clinical coronary heart disease and in the relatives of the group of matched controls It was found by Gertler and White that a significantly higher percentage of the fathers of men with coronary heart disease below 40 years had had cardiovascular disease or had died of cardiovascular disease than of the fathers of the matched control group The trend was in the same direction for the mothers of the men with coronary disease below the age of 40 years as compared with the mothers of the men in the matched control group, although the total number of cases of cardiovascular disease among the mothers was too small to be statistically significant Similarly, it was found that the brothers of the men with coronary heart disease below 40 years showed a higher reported incidence of cardiovascular disease than did brothers of the men in the matched control group The general conclusion that would be drawn from the study of the Gertler and White material is that cardiovascular disease is significantly more frequent in the families of men who suffer coronary disease below the age of 40 years than in men of the same age group free of overt coronary heart disease Unfortunately, one major failing

system rather than arteriosclerosis of the vascular system. There does not exist a valid justification for differentiation of the vascular lesions in the individuals in xanthomatotic families with massive lipoprotein elevation from the arteriosclerosis which occurs in the population-at-large. These special individuals are developing such vascular disease very rapidly, associated with their extremely high levels of the various lipoprotein classes, but inasmuch as their lipoproteins appear to be of the same chemical types as those that occur in individuals of the population-at-large[35], the disease in their arteries hardly deserves the special termination, xanthomatosis of the arteries. What every physician would like to know is the extent to which familial factors may operate in coronary heart disease *in the population-at-large* rather than in coronary heart disease in these special families. A sound evaluation of this issue requires careful studies of one or more types. A careful study could be undertaken to determine the incidence rate of coronary heart disease in siblings of persons in the population-at-large who have demonstrated premature clinical coronary disease instead of the incidence in siblings of selected persons from known xanthomatotic or hyperlipoproteinemic famlies. A similar study could be undertaken to determine the history of coronary heart disease in the parents of a representative sample of persons with clinical coronary heart disease selected out of the population-at-large. Thirdly, the problem can be approached in a different manner by a correlation study of the family history of various individuals in a large population sample with those factors known to be associated with coronary heart disease. Since the level of certain lipoproteins and the blood pressure are such factors, it is important to measure the extent to which either is related, if at all, with the family history of coronary heart disease. As a variant of this study measurements of the lipoproteins in the families of a large number of individuals chosen at random out of the population-at-large can be made to determine whether or not there exists a correlation in lipoprotein levels for family members in general such as is known to exist in markedly hyperlipoproteinemic and xanthomatotic families. Some real progress has been made in several of these

may have biassed the outcome of the family history surveys. To be sure, the size of the difference in familial incidence of cardiovascular disease between Yater's myocardial infarction survivors and his traumatic injury control group is so large that a considerable bias could be tolerated with appreciably altering his conclusions concerning family history of cardiovascular disease. Both studies should be regarded as providing highly suggestive evidence, evidence that should be supplemented by approaches free of the potential bias inherent in retrospective questioning.

A totally different avenue of approach is to determine certain bio-chemical or physiological variables in a representative sample of the population-at-large and, *independently*, to determine the family history of longevity and cardiovascular disease for the same persons. If the biochemical or physiological variables are themselves known to be factors in coronary heart disease, any correlations observed would be of extreme interest. Such a study is free of the objections inherent in that of the retrospective questioning of individuals with coronary disease, since the determination of the biochemical variable, such as the lipoprotein level, and of the physiological variable, such as the blood pressure, is wholly independent of the questioning of the individuals. Furthermore, since the individuals do not know either their blood pressure value or their lipoprotein findings, there is no chance for biassing in a direction either for or against a history of familial cardiovascular disease with unfavorable values of the particular variables under consideration. We may be sure that in such [illegible]

pro [illegible]

sam[illegible] discovered. This is so because of the existence of the well-known special families previously described with either the S_f 0-20 lipoprotein elevation or with the S_f 20-400 lipoprotein elevation. Inasmuch as such categories of individuals are known to have a high incidence of cardiovascular disease in their families, any such cases in the population sample make for the positive association. The question at hand is to what extent such families are represented in a cross-sectional survey of the population-at-large. It is certain that many such families have not been recognized and will be discovered in any cross-section of the

characterizes studies of this type, a failing which was carefully alluded to by Gertler and White and in their publication, namely that this is in essence a *retrospective study* involving the questioning of a group of individuals who have coronary disease themselves and a group without such disease. Inasmuch as it is common for patients with a particular disease to be seeking possible explanations for their own disease, it would not be surprising if the men who had clinical coronary heart disease below the age of 40 years might be more likely to remember the occurrence of such disease in members of their family. Alternatively, if the diagnosis had been in doubt for members of their families, they might well be inclined to have remembered better the possibility that such a diagnosis was one of cardiovascular disease. Any such effects operating for the patients with clinical coronary heart disease would tend to make coronary or cardiovascular disease appear more frequent in their relatives, thus having the effect of biassing the result in the direction of the outcome that was observed.

Yater and co-workers[22], in their classic studies of 866 cases of men with coronary heart disease between the ages of 18 and 39 years, made observations analogous to those of Gertler and White. They questioned 392 men who had survived a well-documented, typical attack of myocardial infarction while in the Army and they questioned a control group of 210 men (amputees or those hospitalized for gunshot wounds) concerning family history of heart disease Hypertension and/or coronary artery disease was reported for the immediate family of 41% of the myocardial infarction cases, whereas these entities were reported in only 13% of the traumatic injury control group of men In the "immediate" family Yater includes father, mother, brothers, and sisters. The conclusion is the same as that arrived at by Gertler and White, but unfortunately the defect in the study is identical with that in the study of Gertler and White, namely the possible biassing of results due to awareness of coronary heart disease as a problem amongst the myocardial infarction survivors.

Unfortunately in both the studies of Gertler and White and those of Yater and co-workers, it is virtually impossible to determine the extent to which the retrospective features of the studies

exclude such listed causes as accidental death or suicide. However, it is entirely possible that a sudden coronary occlusion could have led to a fatal accident and that illness such as coronary heart disease could have been a factor contributing to suicide. Therefore it seems most reasonable to test for differences in lipoprotein levels, Atherogenic Index values, and blood pressures between the group of men reporting one or both parents dead as of the examination time and the group of men both of whose parents were alive at that time without any exclusion. In additional special consideration was given to the group reporting death due to heart disease in either the mother or father. Since often the person is unable to state what type of heart disease was the cause of death in the parent, the overall category "heart disease" was utilized. Any effects observed that are provably significant will, no doubt, be *underestimated*, for heart disease other than coronary heart disease would not be anticipated to be associated with lipoprotein levels[38]. For example, rheumatic heart disease shows no association with lipoproteins. Thus this entire approach is a conservative one aimed at discovering at least any *minimum* familial aspects of coronary heart disease.

THE LIPOPROTEIN AND ATHEROGENIC INDEX VALUES IN RELATION TO FAMILY HISTORY

Of the 878 men between 30 and 39 years under study, 421 men reported that *either the father, the mother*, or both were dead at the time of examination whereas 457 men reported that both parents were alive at the time of examination. The mean value for all lipoprotein classes, for the Atherogenic Index, for the diastolic blood pressure, and for the ages of the men in both groups are presented in Table XVIII. It is noted that the average age of those men reporting one or both parents dead is 34.5 years, whereas the average age for those men reporting both parents alive is 33.7 years. Therefore it is appropriate to make the small correction in all values for the latter group for the 0.8 year difference in average age. When this is done, the values for each class of lipoproteins and the Atherogenic Index values,

population-at-large. The extent to which such cases will be diluted out by the very much larger group of cases not characterized by extreme derangement of lipoprotein levels or to which such cases will be supplemented by cases with a mild lipoprotein derangement, familial in origin, cannot be predicted in advance. However, a *mild* derangement in a biochemical variable or physiologic variable associated with familial cardiovascular disease should manifest itself by a shift in all parts of the distribution of cases on the particular variable to higher values for the group with a positive family history of cardiovascular disease. If the only derangement that exists is that in families with the massive defect, this would manifest itself instead as just a small number of cases in a tail of the distribution curve.

An investigation of precisely this type has now been completed[37], including lipoprotein measurement, blood pressure measurement, and a family history evaluation for 878 employed men between the ages of 30 and 39 years. Blood was taken for lipoprotein analysis and blood pressure measurements were made in the course of routine periodic medical employment examinations, the individual being completely unaware that any such research studies were involved. In a separate part of the same examination all individuals were asked to fill out a routine questionnaire concerning the presence or absence of heart disease or other diseases in their families and the cause of death if their parents were dead. Numerous possible subdivisions of family history are of interest in this type of study. While it would be ideal to have available documented histories concerning coronary heart disease in the parents of the population sample under study, this ideal is very difficult to achieve in practise. Most individuals have only a general idea of cause of death in their parents, especially if such death had occurred several years ago. One major criterion that is reliable is the determination of whether or not the parents are dead or alive for all the subjects under study. Beyond this the information obtained becomes progressively more vague. Such statements as "dead of natural causes" can mean just about anything, but many individuals know no more than this as a cause of death in their parents. In the group of deaths, it might at first thought seem reasonable to

the difference in values, and the significance test upon this difference are as listed below.

	One or Both Parents Dead	Both Parents Alive (Corrected for Age)	Difference	Significance Test
S_f 0-12 lipoproteins	360.5	351.0	9.5	Not significant
S_f 12-20 lipoproteins	53.0	50.8	2.2	Not significant
S_f 20-100 lipoproteins	97.0	90.5	6.5	$p \approx 0.1$
S_f 100-400 lipoproteins	57.9	48.2	9.7	$p \approx 0.02$
Atherogenic Index	72.4	68.1	4.3	$p < 0.01$

The Atherogenic Index, which expresses the composite important information, is clearly higher for the group with one or both parents dead than for the group with both parents alive, even after correction for the slight age difference between the groups (less than one chance in 100 that random sampling would give rise to this large a difference). Therefore a family history of longevity is definitely associated with lower average Atherogenic Index values in the offspring. One possible objection must be considered. This is the possibility that the group with deaths in the parents may on the average be represented by parents who had their children at a later period in life. But this cannot be of any consequence since by separate test it has been shown that the lipoprotein values and Atherogenic Index values in offspring are the same independent of whether either or both parents are in their twenties, thirties, or forties at the time of birth of their offspring. Therefore, the only conclusion is that a family history of early death in one or both parents is associated with higher average Atherogenic Index values in the offspring.

The next question worthy of consideration is whether the observed, significant effect occurs because of a *few individuals* with very high lipoprotein-atherogenic index values or because of a *general* shift toward higher values in the offspring of parents who die at a relatively early age. One good test of this is a determination of the fraction of parents dead for offspring in each Atherogenic Index category. If the fraction of dead rises smoothly with increase in A.I. values even in the moderate A.I. value ranges, it can be inferred that a general shift exists rather than that all the effect is due to the presence of a small number

TABLE XVIII

THE RELATIONSHIP OF PARENTAL LONGEVITY WITH LIPOPROTEIN LEVELS, ATHEROGENIC INDEX VALUES AND DIASTOLIC BLOOD PRESSURES IN OVERTLY HEALTHY 30-39 YEAR OLD MEN

GROUP	*Number of Cases*	*Mean Age (years)*	*Mean S_f0-12 (mg/100ml)*	*Mean S_f12-20 (mg/100ml)*	*Mean S_f20-100 (mg/100ml)*	*Mean S_f100-400 (mg/100ml)*	*Mean A.I. Value (units)*	*Mean Diastolic Blood Pressure mm Hg*
Men Reporting Both Parents Alive	457	33.7	348.6	50.0	88.9	47.0	67.3	69.2
Men Reporting One or Both Parents Dead (Death of all causes)	421	34.5	360.5	53.0	97.0	57.9	72.4	70.6

TABLE XX

THE RELATIONSHIP OF A HISTORY OF FATHER'S DEATH OF HEART DISEASE WITH LIPOPROTEIN LEVELS, ATHEROGENIC INDEX VALUES, AND DIASTOLIC BLOOD PRESSURE IN OVERTLY HEALTHY 30-39 YEAR OLD MEN

GROUP	*Mean Age (years)*	*Mean S_f0-12 (mg/100ml)*	*Mean S_f12-20 (mg/100ml)*	*Mean S_f20-100 (mg/100ml)*	*Mean S_f100-400 (mg/100ml)*	*Atherogenic Index (units)*	*Diastolic Blood Pressure (mm Hg)*
All 878 Men Studied	34.1	354.3	51.5	92.7	52.2	69.7	69.9
122 Men Reporting Father was Dead of Heart Disease	34.6	366.6	54.2	110.0	75.0	78.5	72.5

of individuals with very high Atherogenic Index values. Such data are presented in Table XIX. It is evident that at least above 70 A.I. units the fraction dead is rising smoothly with increasing A.I. values, indicating that short-lived parents are associated with a *general shift* toward higher A.I. values in offsprings, rather than with the presence of a relatively small proportion of off-springs with extremely high A.I. values. The relationship of A.I. value in offspring to longevity in parents is by no means small, since comparison of the group with A.I. values above 110 units with the group having A.I. values below 60 units shows a 52% increase in the fraction with one or both parents dead (0.64 compared with 0.42).

Of the 421 men in the 30-39 year age group studied, 122 men reported the father to be dead of heart disease. A highly rigorous test of the association of death of a father due to heart disease with elevation of lipoprotein level of Atherogenic Index value is to determine whether the 122 men with fathers dead of heart disease show significantly different levels from all other persons in the group (878-122, or 756). The data necessary for this comparison are presented in Table XX. The men with

TABLE XIX

RELATIVE PROBABILITY OF HAVING ONE OR BOTH PARENTS DEAD IN RELATION TO ATHEROGENIC INDEX VALUES IN 30-39 YEAR OLD MALE OFFSPRING

Atherogenic Index Range (units)	*Fraction of Subjects Having One or Both Parents Dead*	*Relative Probability of Having One or Both Parents Dead (setting value = 1.00 for A.I. values below 40 units)*
< 40	23 out of 25, or 0.42	1.00
40-49	50 out of 120, or 0.42	1.00
50-59	71 out of 162, or 0.44	1.05
60–69	65 out of 154, or 0.42	1.00
70-79	71 out of 145, or 0.49	1.17
80-89	52 out of 94, or 0.55	1.31
90–99	31 out of 59, or 0.53	1.26
100 or higher	46 out of 80, or 0.58	1.38
110 or higher	36 out of 56, or 0.64	1.52
130 or higher	21 out of 28, or 0.75	1.79

For men of 35 years of age with A.I. values over 110 units there is approximately a five-fold greater fraction of fathers already dead of heart disease in comparison with the fraction of fathers dead of heart disease for 35 year old men with A.I. values below 50 units.

A similar test was carried out to determine any possible association of death of the mother of heart disease with lipoprotein and Atherogenic Index values in the offspring. Unfortunately for this test, but expectedly, the number of men out of the total of 878 with mothers dead of heart disease was only 31 cases While the Atherogenic Index was higher (75 0 units) for the men whose mothers were dead of heart disease than for the overall group of 878 men (69.7 units), the number of cases available did not allow for proof that this difference in A I. values was significant However, the class of lipoproteins which had shown the most striking elevation in level for men with fathers dead of heart disease, the S_f100-400 lipoproteins, *could* also be proven significantly higher for the men whose mothers were dead of heart disease than for the men in the overall group, ($p = 0.02$)

TABLE XXI

RELATIVE PROBABILITY OF HAVING FATHER DEAD OF HEART DISEASE IN RELATION TO ATHEROGENIC INDEX VALUES IN 30 39 YEAR OLD MALE OFFSPRING

Atherogenic Index Range (units)	*Fraction of Subjects Having Father Dead of Heart Disease*	*Relative Probability of Having Father Dead of Heart Disease (setting value = 1.00 for A I values below 40 units)*
< 40	3 out of 56, or 0 054	1 00
40-49	14 out of 121, or 0 116	2 15
50-59	17 out of 165, or 0 103	1 91
60 69	18 out of 156 or 0 115	2 13
70 79	26 out of 147, or 0 179	3.28
80 89	9 out of 95, or 0 095	1.76
90 99	14 out of 60, or 0.233	4.32
100 or higher	21 out of 80, or 0.263	4 87
110 or higher	16 out of 55, or 0.291	5.39
130 or higher	11 out of 28, or 0.393	7.28

fathers dead of heart disease were on the average 0.5 years older than the overall group of 878 men (34.6 years versus 34.1 years). The various lipoprotein values and the Atherogenic Index values are readily corrected for this 0.5 year age difference. The age-corrected values and the difference between the overall group of men and that part of the group with fathers dead of heart disease, together *with significance tests of such differences are listed* below:

	Overall Group	*Father Dead of Heart Disease*	*Difference*	*Significance Test*
	(Corrected for 0.5 Year Age Difference)			
s_f0-12 lipoproteins =	354.3	365.1	10.8	Not significant
s_f12-20 lipoproteins =	51.5	53.7	2.2	Not significant
s_f20-100 lipoproteins =	92.7	109.0	16.3	$p < 0.001$
s_f100-400 lipoproteins =	52.2	74.2	22.0	$p < 0.001$
Atherogenic Index =	69.7	78.0	8.3	$p < 0.001$

These data leave little question but that the group of men whose fathers are already dead of heart disease are quite different in lipoprotein and Atherogenic Index values, from the overall *group of men of the same age (For the Atherogenic Index,* the chance that random sampling could have given rise to the observed difference is less than one in 1000). Here again it is of interest to know whether the effect is accounted for by a relatively small proportion of men with extremely high Atherogenic Index values or whether it is a continuous effect operating over the entire range of Atherogenic Index values encountered. In Table XXI are presented the data concerning the fraction of men in the overall group whose fathers are dead of heart disease ranked by Atherogenic Index value of the offspring. Inspection of those data indicates clearly that the effect is a smoothly *continuous one over essentially the entire* Atherogenic Index range, with a rising fraction dead of heart disease with rising Atherogenic Index value. Thus the effect is not accounted for only by a small group of men with very high Atherogenic Index values. The comparison of the death rate due *to heart* disease in fathers of men with high Atherogenic Index values with that for men with very low Atherogenic Index values is startling.

nary heart disease and a family history of heart disease. Furthermore, such evidence is free of any of the possibilities of retrospective bias that may characterize questioning men with coronary heart disease concerning the presence or absence of heart disease in their families. In this study of lipoproteins, Atherogenic Index and blood pressure levels versus family history, there is no knowledge available to the experimental subject concerning these measurements that might have conceivably biassed his reply to the questionnaire concerning family history. It is of interest that these studies, free of the possibility of retrospective bias, do lead to precisely the same type of conclusion arrived at by Yater and co-workers and independently by Gertler and White through their retrospective studies of the family history in young men with coronary heart disease

POSSIBLE MECHANISM OF MEDIATION OF EFFECT OF FAMILY HISTORY UPON ATHEROGENIC INDEX VALUES

Establishment that the 30-39 year old offspring of fathers who die prematurely of heart disease show higher Atherogenic Index values than do members of the overall 30-39 year population sample leads immediately to the question of how such an effect is mediated A familial relationship can be on a hereditary, or genetic, basis or it can be the result of environmental features common to the members of a particular family It is sometimes a matter of no little difficulty to distinguish these two mechanisms Further, the situation may even be complicated by the inheritance of a trait that alters the offspring's response to a particular environmental influence

In subsequent chapters two features of humans associated with lipoprotein-Atherogenic Index alteration will be discussed in detail These are the degree of overweight and the cigarette smoking habit. There are elements in both these features that suggest familial factors may be of consequence Overweight may conceivably be associated with hereditary tendencies to hypometabolism, or to overeating, or with familial patterns of overeating [illegible]

at least, [illegible]

THE BLOOD PRESSURE IN RELATION TO FAMILY HISTORY

All the considerations above apply to one major factor involved in the development of coronary heart disease, namely the lipoprotein-Atherogenic Index value The diastolic blood pressure level is, from previous discussion (See Chapter IV), the other major factor involved in determination of coronary heart disease risk. Hence any possible relationship of blood pressure in offspring with family history of early death or of heart disease specifically is of importance. In Table XVIII are presented the data for the diastolic blood pressures in the 421 men with one or both parents dead and for the 457 men with both parents living It is not possible to show, from these data that the diastolic blood pressure is significantly different for those men with parental history of early death as compared with a parental history of longevity. The second pertinent comparison is that for the 122 with fathers dead of heart disease with the overall group of 878 men. This comparison is tabulated below.

	Mean Age (Years)	Mean Diastolic Blood Pressure (mm Hg)
122 men with fathers dead of heart disease	31.6 years	72.5 mm
878 men (overall group)	31.1 years	69.9 mm

After correction for the 0.5 year difference in age for the group with fathers dead of heart disease (a correction of 0.2mm), the difference between this group and the overall group is 72.5-70.1, or 2.4mm. While this is a small difference in mean diastolic blood pressure, the large number of cases available allows one to be sure that there is less than one chance in 100 that this difference in blood pressures would be observed as a result of random sampling Therefore there is a low degree of positive association of elevation of diastolic blood pressure in the offspring with the history of death of the father of heart disease. The magnitude of the effect is certainly less than that observed for the Atherogenic Index.

The evidence presented here is strong that a positive association exists between two known factors predisposing to coro-

or environmental mechanism, or some combination thereof, cannot be determined within the framework of this evidence.

The 122 men with a paternal history of death from heart disease smoked, on the average, 10.1 cigarettes per day. The overall group smoked, on the average, 9.9 cigarettes per day. Therefore, there is *no evidence* that would suggest that any of the association between lipoprotein level elevation and paternal history of heart disease is at all mediated by a tendency to smoke cigarettes.

THE PRACTICAL CLINICAL IMPLICATION OF ASSOCIATION OF ATHEROGENIC INDEX VALUES WITH FAMILY HISTORY OF HEART DISEASE

That a parental history of heart disease is associated with a significant elevation in Atherogenic Index value and to a lesser extent in diastolic blood pressure in offspring can now be accepted as well documented Therefore, there is every reason to expect a higher *incidence* of coronary heart disease in persons whose parents had heart disease at a relatively early age than in persons without such a parental history Further, from the data relating Atherogenic Index and blood pressure to risk of future coronary heart disease, the precise extent to which a positive family history increases the average risk of coronary heart disease in offspring could readily be estimated. Unfortunately, however, no really satisfactory unbiassed data are available to determine directly how large this association is in the population-at-large. Thus, while a higher *incidence rate* of coronary heart disease is definitely to be expected in the offspring of persons with heart disease, it is not possible at this time to state whether or not the Atherogenic Index plus blood pressure findings account for the totality of such association as does exist. In any event the evidence for the effect of family history operating via these mechanisms is solidly based and free of speculation or bias. The available evidence does not allow for a statement that no other possible mechanisms might exist in addition although no comparably documented evidence supports such other possible mechanisms One possible factor that has been suggested by several workers

of a family environment that leads to smoking. For overweight persons, there does exist an average elevation in Atherogenic Index arising primarily from an association of overweight with S_f20-100 and S_f100-400 lipoprotein levels. For cigarette smokers the most prominent effect upon Atherogenic Index arises through the association of cigarette smoking with elevation of S_f0-12 lipoprotein levels.

The elevation in Atherogenic Index in the 122 men who reported the father dead of heart disease is predominantly associated with elevation in S_f20-100 and S_f100-400 lipoprotein levels. The smaller degree of elevation of S_f0-12 lipoprotein levels could not be proved significant within the existing data. These findings suggest that it would be worthwhile to know whether these 122 men are overweight relative to the overall group, and possibly whether they are heavier smokers. Degree of overweight is expressed in terms of the value known as the relative weight, which is the person's actual weight divided by the ideal weight for his height. *(See Chapter IX.)* The average relative weights for those with a father dead of heart disease and for the overall group of men are as follows.

For 122 men with father dead of heart disease, Relative Weight = 1.092
For 878 men in the overall 30-39 year old population sample,
Relative Weight = 1.044
Difference = 0.048

On the relative weight scale, the men whose fathers are dead of heart disease are 5% heavier than the overall group. A statistical test of this difference shows that a difference this large would arise by sampling errors less than once in 10,000 times. It can therefore be concluded that the men whose fathers died of heart disease are heavier for their height than are the men in the overall group. From the data of Table XXXII this degree of increase in relative weight would be expected, on the average, to lead to an elevation in Atherogenic Index of 2.9 units. The observed elevation for the 122 men with fathers dead of heart disease is 8.3 units. Therefore, approximately 35% of the elevation in Atherogenic Index would be expected from their degree of overweight. Whether the relationship of overweight with history of paternal death of heart disease operates via a hereditary

group whose fathers were already dead of heart disease. Inspection of these data shows immediately that in spite of the *shift in distribution* of Atherogenic Index values to high values, there are many individuals in this group characterized by low Atherogenic Index values, values lower than average for the overall population of persons of this age group. Entirely similar considerations apply to the diastolic blood pressure findings. If a person has essentially "escaped" the family history effect, namely, if he has a moderate or low Atherogenic Index and a moderate or low blood pressure value, there exists no evidence whatever that he need fear premature coronary heart disease solely because of an unfavorable family history of such disease. Even in the families characterized by one or another of the massive defects in blood lipoprotein levels, such as marked s_f0-12 lipoprotein elevation or s_f20-400 lipoprotein elevation, an appreciable fraction of the members of the family "escape" the inherited defect. Thus, when a father shows the lipoprotein derangement, it is common to find that a daughter may show the derangement too, but that one or more sons do not. Alternatively a son or several sons may show the derangement whereas none of the daughters show it

The crucial clinical issue in all of this is that the physician can be, if he chooses, vastly more precise in his *prognostic evaluation* of the meaning of an unfavorable family history of heart disease in a particular patient. It is neither correct medically nor good clinical medicine to issue a poor prognosis for future coronary heart disease risk to a patient simply because of an adverse family history It is not correct to inform a patient that his outlook is unfavorable "because he has chosen his ancestor's unwisely" Many such persons have far lower risks of future coronary heart disease than the "average" man in the population and this most favorable news can be transmitted to such a person by the physician who utilizes the modern, simple methods of obtaining the requisite information.

Nor should errors of the opposite type be made clinically. It does follow, from the evidence at our disposal, that a favorable family history of freedom from premature heart disease means, on the *average*, a lower risk of future coronary heart

is the inheritance of some type of defective coronary vascular tree in persons with a positive family history of early coronary heart disease. Suggestions have been made that either the intimal thickness of the coronary arteries or anatomical pecularities such origin of the arteries or kinking might be hereditary predisposing factors. These are but speculations, wholly unsupported by any evidence and hence hardly deserving of consideration in the practical clinical matter of dealing with patients.

While the evidence is conclusive that a family history of heart disease does, *on the average*, predispose the offspring to coronary heart disease via the lipoprotein and blood pressure mechanisms, it cannot be stressed too much that this is an *average* predisposition. By no means does every person with a family history of premature heart disease show the elevation in Atherogenic Index or diastolic blood pressure that characterizes the group as a whole. In Table XXII is presented the distribution of Atherogenic Index values for the 122 men in the 30-39 year age

TABLE XXII

DISTRIBUTION OF ATHEROGENIC INDEX VALUES FOR 122 MEN (30-39 YEAR AGE GROUP) WHO REPORT THEIR FATHERS ARE DEAD OF HEART DISEASE

Range of Atherogenic Index Values (units)	*Number of Men Who Reported Father Dead of Heart Disease*	*Number of Men Who Report a History Other Than Father Dead of Heart Disease*
Below 40	3	53
40-49	14	107
50-59	17	148
60-69	18	138
70-79	26	121
80-89	9	86
90 99	14	46
100-109	5	18
110-119	4	16
120-129	1	6
130-139	6	2
140 or higher	5	15
TOTAL	122	756

Chapter VII

THE RELATIONSHIP OF AGE WITH CORONARY HEART DISEASE

THERE is no doubt whatever that the attack rate of clinical manifestations of coronary heart disease increases with increasing age in the American population, both in the male and female sex. The United States Vital Statistics reproduced below in Table XXIII, clearly indicate the startling and definite rise in incidence of clinical coronary heart disease with increasing age for both sexes. There exist in the clinical literature some erroneous impressions concerning the relative frequency of coronary heart disease at various ages. Thus, from the analysis of the age distribution of cases of myocardial infarction in office practice or in consecutive hospital admissions, many authors have commented upon the fact that a particular age bracket, for example 50 to 59 years, appears to be that in which persons are especially prone to develop clinical coronary heart disease, simply

TABLE XXIII

FATAL CORONARY HEART DISEASE INCIDENCE RATE IN NUMBER OF PERSONS PER 100,000 PER YEAR IN THE UNITED STATES

(From U. S. Vital Statistics, 1949)

Age Group (years)	*Fatal Coronary Heart Disease Incidence Rate in Cases per 100,000 per persons per year*	
	Men	*Women*
35	49	11
45	200	52
55	656	205
65	1705	753

disease because of a lower *average* Atherogenic Index and diastolic blood pressure. But many individuals with an excellent family history of freedom from heart disease can and do show high Atherogenic Index and blood pressure values in spite of the average trend. Therefore re-assurance of a patient of a bright outlook for freedom from coronary heart disease simply because of a good family history represents poor clinical medicine, for it may deny the individual the opportunity to discover the basis for a seriously high risk of future coronary heart disease and to take, in time, those steps which might reduce the risk appreciably.

have had recourse to a superficial device for solving the problem of the increasing frequency of clinical coronary heart disease with increasing age. They have stated simply that coronary heart disease in the older age groups is a different disease from coronary heart disease in the younger age groups. With this statement being made equivalent to a definition, the difference in frequency of the disease between the older age group and the younger age group requires no special explanation. Actually, however recourse to such an explanation would mean that not just two diseases must be accounted for, but rather, many diseases, for the increasing frequency of coronary disease with aging operates all the way from the third decade of life up through at least the eighth decade of life. If the device is used of renaming the disease as a different entity in the older age group from that in the younger group, it would be quite appropriate to state that for every ten year age span there is a different disease with which we are dealing. Carried to extremes it could be stated that there is a different "coronary disease" at every year of life in order to explain increase in frequency with change in age. It is important to note that neither clinical nor pathological evidence suggests any significant difference in the basic picture of clinical coronary heart disease between that seen at one age and at another It is not surprising that there may be minor differences in the clinical picture of coronary heart disease in a 75 year old man from that in a 25 year old man, since physiologically there are many features that are different in men in the 75 year age group from men in the 25 year age group. The central pathological feature noted is that of coronary artery narrowing due to an accumulation of material within the intima, a feature that has been found to characterize myocardial infarction autopsy material all the way from 18 out to 80 years of age.

Before considering in detail the evidence with respect to coronary heart disease itself, some general concepts should be delineated concerning diseases which show an increasing frequency with increasing age, especially in relationship to the evaluation of factors conceivably responsible for these observed trends The basis for a disease may be primarily a factor which operates *instantaneously*. An illustration of this would be a sit-

because this age bracket contains a larger number of their cases than any other single age bracket. Such statistics are grossly misleading, for they fail to take into account the *size of the population at risk* in the various age categories. Thus, if there are many more men in the population in the age group, 50-59 years, than there are in the age group, 70-79 years, there may be more hospital admissions due to coronary disease in the 50-59 year age group than the 70-79 year age group even though the risk of coronary heart disease is much higher per thousand persons per year in the older age group. Data concerning the frequency of coronary heart disease in relationship with age can only be meaningful if they are expressed in reference to the population at risk, namely in terms of the attack rate, or the number of cases, per thousand persons at risk per year or per 100,000 persons at risk per year rather than in terms of absolute number of cases admitted in a hospital per year So well known is the relationship between increase in frequency of coronary heart disease with increasing age that many writers have in the past drawn the erroneous conclusions that age is *the* factor in the development of coronary heart disease and that coronary heart disease is an inevitable accompaniment of aging To be sure, the relationship of clinical coronary heart disease incidence with increasing age is highly impressive, but it by no means justifies the statement that age is *the* factor or the most important factor involved, nor does it justify a concept of the inevitability of development of clinical coronary heart disease with increasing age The phenomenon of occurrence of serious or fatal myocardial infarction in 35 year old men and even in 25 year old men no longer excites the special interest that it once did, for we now know that many men develop such serious disease even before the age of 35 years The recent experience of Yater (during World War II) in accumulating a series of over 800 documented cases of myocardial infarction in men between the ages of 18 and 39 years is eloquent testimony to the all-too-great frequency of coronary heart disease even at relatively early ages

The increasing frequency of coronary heart disease with increasing age demands explanation in an over-all concept of the nature of the evolution of this important clinical entity. Some

increased. This is true simply because for a process which operates by accumulation over time there would be a greater *accumulation* of the sub-clinical disease in 20 years than there would be in ten years, in 30 years a still greater accumulation, and in 40 years an even greater accumulation. In a hypothetical case such as this it would be wholly incorrect to make the statement that the blood sugar level had not been important in the development of the disease simply because its average level remained the same with increasing age. It could very well be the total or predominant cause of the disease. As a general procedure for demonstrating that a factor which operates in this particular manner is important for a disease, a group of individuals all at a particular age can be studied. If it is found that those who show the higher levels of the particular factor have more of the disease under consideration than do those who show low levels, this would represent strong evidence to implicate the level of the factor in the disease

The application of simple logic will often enable one to determine the manner in which a particular factor is associated with a particular disease and indeed to determine whether or not one is dealing with an *instantaneous* or an *accumulative* type of factor It is often readily possible to show that particular factors cannot possibly operate in one of the two ways, e.g., as an instantaneous factor, because assumption that it does would lead to results highly inconsistent with observational material, which of course (if properly observed) must be correct. At times, it may not be possible from a single item of evidence to make the determination of whether an instantaneous factor or an accumulative factor is at hand, but with consideration of several segments of the evidence a consistent picture may emerge for one type of factor, e g the accumulative one, but a highly inconsistent picture for the other, e.g., the instantaneous one, in which case the choice of the nature of the factor becomes quite clear—at least quite clear as a working hypothesis for further consideration.

The specific problem of sub-clinical and clinical coronary heart disease may now be considered in the light of these general principles The detailed evidence that the lipoprotein-Atherogenic Index and the blood pressure are two major factors

uation where an acutely toxic substance is ingested and instantaneously produces clinical manifestations. In this case there would be no accumulation of illness over previous weeks, months, or years. A second possible type of illness would be that where some factor operates, not instantaneously, but rather over a period of time. With longer periods of time passed the greater is the accumulation of the sub-clinical aspects of the disease and hence the greater the chance of expression of the disease in clinical form. In this latter case the factor responsible can be considered to be expressive of the *rate* at which sub-clinical disease accumulates, whereas the total *amount* of accumulated disease would be expressed by the multiplication of this rate factor and the time period over which it has operated. Lastly, in a complex disease process, there might be a combination of those factors which operate instantaneously and those factors which operate over a period of time to produce accumulation of disease at the sub-clinical level If a factor operates instantaneously in the production of a disease, explanation of an increasing frequency of this disease with increasing age would require that there must either be, if the factor is a presence-versus-absence factor, a progressively greater number of individuals in the population who possess this factor as age increases, or if the factor is universally present but at different levels in different individuals, there must be a sufficient increase in the percentage of individuals with high levels of this factor with increasing age in order to explain the age trends observed. On the other hand, for a factor which is expressive of the *rate* at which sub-clinical disease develops, it is possible for both the level of the factor and the fraction of the population characterized by each such level to remain constant over the entire usual life span of individuals and still be consistent with an increasing trend of mortality from the disease with increasing age. Thus, for example, *if* the level of blood sugar were known to have the same distribution and the same average level for every age in life and *if* it were also known that the level of blood sugar were expressive of the rate at which some disease develops sub-clinically, it would be expected that the overt expression of that disease would increase with increasing age even though the blood sugar level remained the same as age

that (1) the Atherogenic Index *cannot* operate primarily as an instantaneous type of factor, (2) that it would be consistent with the observed facts to consider the possibility that the Atherogenic Index operates as an *accumulative* type of factor and (3) the possibility deserves consideration that the Atherogenic Index may still operate as an instantaneous factor but some unknown, hypothetical, undiscovered factor operates as a major accumulative factor. Attention may now be turned to the blood pressure as a factor with demonstrated ability to predict the risk, or attack rate, of clinical coronary heart disease. Does the blood pressure operate as an instantaneous factor in producing risk of clinical coronary heart disease or as an accumulative factor? In Table XIV is presented the relative risk, or attack rate, of coronary heart disease for various values of the diastolic blood pressure. In order to explain a 35-fold increase in coronary heart disease attack rate that is observed for 65 year old men versus 35 year old men it would be required that the average diastolic blood pressure for 65 year old men be much higher than 150 mm Hg compared with the average of 71 mm Hg for 35 year old men. This, however, is clearly not the case since the blood pressures are 76 mm Hg and 71 mm Hg for the two age groups, respectively. Therefore, it is clearly inconsistent with reality to assume that blood pressure *can* be operating as an instantaneous factor to explain the difference in attack rate of coronary heart disease for these two age groups assuming the blood pressure *to* operate as the only or major factor in determining the risk. The conclusions we can draw from this are: (1) the blood pressure cannot possibly be described as an *instantaneous* factor to explain the marked increase in coronary heart attack rate with increasing age (2) it would be consistent with the evidence for the blood pressure to operate in an accumulative fashion producing the risk of clinical coronary heart disease; and (3) it would still be consistent that the blood pressure operates instantaneously but that some unknown, hypothetical, undiscovered factor oprates in an accumulative fashion Lastly the possibility must be considered that in some way the blood pressure and the Atherogenic Index might together represent an instantaneously operating factor in the production of risk of clinical coronary heart dis-

in determining the risk of clinical coronary heart disease has been presented. Indeed no other factors have yet been discovered for which positive evidence exists demonstrating an association with the risk of future clinical coronary heart disease that cannot be explained either by their effect on the Atherogenic Index values or by their effect on the blood pressure. This is not to say that no other independent factors will ever come to light. However, it would be highly pertinent, *when and if any such factor* is proposed, to determine carefully whether it represents a truly new and independent factor or whether it is simply another reflection of the action of the blood lipoproteins and/or the blood pressure. It is highly pertinent to evaluate serially both the lipoprotein-Atherogenic Index value and the blood pressure with respect to operation either as instantaneous factors or as accumulative factors.

The risk of clinical coronary heart disease, or the attack rate of clinical coronary heart disease, for various values of the Atherogenic Index in 35 year old men is presented in Table XV. From the U. S. Vital Statistics the separate knowledge is available showing that the coronary heart disease attack rate for 65 year old men is approximately 35 times that for 35 year old men. If the Atherogenic Index value were to be an instantaneously operating factor in determining the risk of coronary heart disease and were the only, or major, factor operating, it should be possible, by inspection of the risk table for 35 year old men, Table XV, to determine how high the average Atherogenic Index would have to be in 65 year old men in order to account for this 35-fold increase in heart attack rate. It is seen that an Atherogenic Index value of more than 150 units would be required for the average 65 year old man if the Atherogenic Index operated as an instantaneous factor and were the only one of consequence. However, studies of numerous samples of the population indicate that the average Atherogenic Index value in 65 year old men is only 68.8 units. This is vastly below the required value of over 150 units. Indeed the Atherogenic value of 68 8 units would give rise to a prediction of no increase in heart attack rate for 65 year old men versus 35 year old men, *assuming instantaneous operation.* Therefore the conclusions must be drawn

that (1) the Atherogenic Index *cannot* operate primarily as an instantaneous type of factor, (2) that it would be consistent with the observed facts to consider the possibility that the Atherogenic Index operates as an *accumulative* type of factor and (3) the possibility deserves consideration that the Atherogenic Index may still operate as an instantaneous factor but some unknown, hypothetical, undiscovered factor operates as a major accumulative factor Attention may now be turned to the blood pressure as a factor with demonstrated ability to predict the risk, or attack rate, of clinical coronary heart disease. Does the blood pressure operate as an instantaneous factor in producing risk of clinical coronary heart disease or as an accumulative factor? In Table XIV is presented the relative risk, or attack rate, of coronary heart disease for various values of the diastolic blood pressure. In order to explain a 35-fold increase in coronary heart disease attack rate that is observed for 65 year old men versus 35 year old men it would be required that the average diastolic blood pressure for 65 year old men be much higher than 150 mm Hg compared with the average of 71 mm Hg for 35 year old men. This, however, is clearly not the case since the blood pressures are 76 mm Hg and 71 mm Hg for the two age groups, respectively. Therefore, it is clearly inconsistent with reality *to assume that* blood pressure can be operating as an instantaneous factor to explain the difference in attack rate of coronary heart disease for these two age groups assuming the blood pressure to operate as the only or major factor in determining the risk. The conclusions we can draw from this are: (1) the blood pressure cannot possibly be described as an instantaneous factor to explain the marked increase in coronary heart attack rate with increasing age, (2) it would be consistent with the evidence for the blood pressure to operate in an accumulative fashion producing the risk of clinical coronary heart disease; and (3) it would still be consistent that the blood pressure operates instantaneously but that some unknown, hypothetical, undiscovered factor oprates in an accumulative fashion Lastly the possibility must be considered that in some way the blood pressure and the Atherogenic Index might together represent an instantaneously operating factor in the production of risk of *clinical* coronary heart dis-

ease. In Chapter V an explanation was given of how one can calculate the risk of clinical coronary heart disease by multiplying together the independent risks from the blood pressure data and from the Atherogenic Index data. We may now consider the case of 35 year old men versus 65 year old men using the products of the two independent risks from the blood pressure and from the Atherogenic Index. It is seen that using the mean values for diastolic blood pressure and Atherogenic Index for 65 year old men versus 35 year old men that the attack rate for 65 year old men would be approximately the same as the attack rate for 35 year old men which is far below the relative attack rates actually observed. Hence the net conclusion that can be drawn from the blood pressure alone, the Atherogenic Index alone, or a risk *accrued from their combination is that neither* of these values alone nor their combination could possibly operate as instantaneous factors in determining coronary heart disease risk. It would still be consistent to consider the possibility that either alone or the two together operate as accumulative types of factors in determining the coronary heart disease risk or that some wholly undiscovered, unmeasured, unknown and hypothetical factor accounts for the age effect in coronary heart disease. Inasmuch as neither alone nor these two factors in combination could consistently explain the observed fact of the age increase of coronary heart disease risk operating as instantaneous factors, attention may be turned to the credibility that either or both may operate as accumulative factors in determination of risk. Before proceeding with this, a major point of scientific method and philosophy must be stated. When evidence is clearly at hand that a given factor is definitely associated with a disease, as such evidence is clearly at hand both for the Atherogenic Index and for the blood pressure with coronary heart disease, it is completely illogical to abandon the test of whether instantaneous operation or accumulative operation of such factors can explain the observed data and to jump immediately to the possibility of a third unknown, hypothetical, undemonstrated, unmeasured factor. It behooves the investigator, as a first step, to test both the instantaneous and the accumulative possibilities for those factors which are known and proven It is only when

and if the factors which are known and proven cannot possibly explain the observations either on an instantaneous or an accumulative basis that some additional factor must be sought. This point continues to escape many investigators. Nature is complicated enough not to require that scientists and medical investigators introduce *needless* additional complications in her understanding. The evidence may be evaluated in these lights, "Is there any inconsistency with observational data if the Atherogenic Index and the diastolic blood pressure are considered as accumulative factors in coronary heart disease risk, and is there ancillary supportive evidence which suggests that such factors do or do not operate as accumulative factors?"

THE ATHEROGENIC INDEX CONSIDERED AS AN ACCUMULATIVE FACTOR

It has been shown that the Atherogenic Index factor cannot operate as an instantaneous factor. Would consistency with observational material be achieved by postulation that the Atherogenic Index operates as an accumulative factor? *Suppose that the Atherogenic Index value of a person operates as an accumulative factor* Under such circumstances one would expect that a particular Atherogenic Index operating for two years would accumulate twice as much toward the risk of coronary heart disease as that same Atherogenic Index operating over one year. Correspondingly, that same Atherogenic Index operating for ten years would accumulate ten times as much toward the risk of coronary heart disease as if such an Atherogenic Index had been operating for only one year The corollary of such reasoning concerning accumulative operation would be that an Atherogenic Index of 150 units will accumulate twice as much toward the risk of coronary heart disease in one year as an Atherogenic Index of 75 units, and correspondingly that an Atherogenic Index of 150 units would accumulate as much in one year as an Atherogenic Index of 75 units would accumulate in two years. Later we will come to discussions of possible more refined modifications of the handling of the time variable, but for the moment this is an adequate approach In Chapters III and V it was

shown (Tables I and XV) that for any particular age group, such as 30-39 year old males, that the Atherogenic Index is markedly increased for those who develop clinical coronary heart disease over those who do not and that there is a rising risk of coronary heart disease with rising Atherogenic Index values. For example, at Atherogenic Index values of 150 units, the future risk of coronary heart disease, or the attack rate of coronary heart disease in cases per thousand per year, will be approximately 11.2 times that for an Atherogenic Index of 75 units.

Would the accumulative operation of Atherogenic Index help explain the marked increase in coronary heart disease in 65 year old men in terms of numbers of cases per thousand per year as compared with 35 year old men? For purposes of evaluation of this concept one can start with simplifying assumptions, and then determine how the concept would be modified by reducing the simplifications. If 75 units of Atherogenic Index operating over two years amounts to the same accumulation of risk as 150 units operating over one year, such reasoning could be extended to state that 75 Atherogenic Index units operating for ten years would give rise to a total accumulation of 750 units, for twenty years to 1500 units, for thirty years, to 2250 units, and for forty years to 3000 units Now let us (for simplification) assume that the average man at age 35 years has had an Atherogenic Index value of 69.7 units for all the 35 years of his life and correspondingly let us assume that the average 65 year old man who has an Atherogenic Index of some 68.8 units had that same value for all of his life. The 35 year old man with an Atherogenic Index of 69.7 units operating over 35 years would have accumulated 35x69.7 or 2,440, units toward his risk of coronary heart disease. The 65 year old average man with a value of 68.8 units operating over 65 years would have accumulated 4,472 units in toto. Now how do these two respective values of the number of accumulated units rate in terms of expected risk of coronary heart disease. This can be approximated by reference to 35 year old men If a man were to accumulate 4,472 units (which is the value for the *average* 65 year old man) in 35 years instead of 65 years, he would have had to have an Atherogenic Index value of 4,472 divided by 35, or 127.8 units The

risk tables (Table XV) show that in 35 year old men an Atherogenic Index of 127.8 units corresponds to 33.3 over 3.77, or 8.8 *times as high a risk* as for the average 35 year old man with an Atherogenic Index of 69.7 units. Thus, whereas consideration of the Atherogenic Index as an instantaneous factor leads to prediction of nearly equal risks for the average 35 year old man and the average 65 year old man, the accumulation concept in its simplest form predicts an 8.8 fold higher risk for the 65 year old man, which is much closer to reality. It is important now to go back to the simplifying approximations that have been applied. It can be demonstrated readily that the simplifying approximations have in no way materially altered the results obtained *through the concept of accumulation*. One of the simplifying approximations made is that the man at 35 years of age with an Atherogenic Index of 69.7 units had this same Atherogenic Index all through the first 35 years of life. It was also approximated

TABLE XXIV

AGE TRENDS IN MEAN ATHEROGENIC INDEX VALUES FOR UNITED STATES MALES AND FEMALES

Age (years)	Atherogenic Index (in units) Males	Females
Birth	(49)	(40)
5	(49)	(40)
10	(49)	(40)
15	49.5	40.5
20	51.5	41.0
25	58.0	41.7
30	64.3	48.6
35	69.7	52.3
40	75.6	55.5
45	79.8	58.5
50	79.7	61.9
55	76.5	64.8
60	73.0	67.3
65	68.8	69.5
70	61.7	71.7

Values in parenthesis are based upon fewer than 25 cases. Hence these values are not stably fixed.

that the 65 year old man with an Atherogenic Index of 68.8 units had this same Atherogenic Index value throughout his entire 65 years. Neither of these approximations could possibly hold for every man in the population for this would mean that the average Atherogenic Index does not change with age. But from direct observation it is known that the average Atherogenic Index does change with age (see Table XXIV). It was shown (Chapter V) that persons tend very strongly to retain their *relative* ranking on the Atherogenic Index scale over a period of years throughout adult life. Thus a 20 year old becoming a 22 year old tends to remain as much above or below average in Atherogenic Index as he was at age 20. Similarly, a 30 year old becoming a 32 year old, a 40 year old becoming a 42 year old, and a 50 year old becoming a 52 year old, all tend to retain their positions relative to persons of the same age categories on the Atherogenic Index scale, assuming they do not change markedly in weight or develop some disease such as diabetes, hypothyroidism, or nephrosis. Therefore the first simplifying approximation, that the Atherogenic Index for a 35 year old man is the same for all the 35 years of his life, may be substituted by an approximation which is extremely close to the truth because of the fact that people retain their relative ranking throughout life. This close approximation would be that a man who at age 35 is average in Atherogenic Index would have had an average value of the Atherogenic Index for all periods in life before that. The *trend in Atherogenic Index values from childhood through the* 8th decade of life is known from direct measurement (See Table XXIV) Therefore *if the average* 35 year old man shows an Atherogenic Index value of 69.7 units, then at 30 years of age his Atherogenic Index would have been 64.3 units, at 25 years, 58.0 units, at 20 years, 51.5 units, at 15 years, 49.5 units, at 10 years, 49 units, and approximately that same value back to the time of birth. Now the total accumulation toward risk of coronary heart disease can be caculated directly This is done by considering successive five year intervals from birth out to the age of 35 years.

For the interval, 0-5 years of age,
Average Atherogenic Index = 49 units, Accumulation is 5x49 = 245 0

For the interval 5-10 years of age, Average Atherogenic Index = 49 units,	Accumulation is 5x49 = 245.0
For the interval 10-15 years of age, Average Atherogenic Index = 49.2 units,	Accumulation is 5x49.2 = 246.0
For the interval 15-20 years of age, Average Atherogenic Index = 50.5 units,	Accumulation is 5x50.5 = 252.5
For the interval 20-25 years of age, Average Atherogenic Index = 54.8 units,	Accumulation is 5x54.8 = 274.0
For the interval 25-30 years of age, Average Atherogenic Index = 61.1 units,	Accumulation is 5x61.1 = 305.5
For the interval 30-35 years of age, Average Atherogenic Index = 67.0 units,	Accumulation is 5x67.0 = 335.0

Now all these five year increments can be summed up, yielding a total accumulation=1,903 units. In an entirely similar manner, the five year increments from birth out to 65 years can be calculated and summed for the average 65 year old man, yielding 4,174 units.

This arithmetic provides the total accumulation for both the average 35 year old man and the average 65 year old man, *without* the simplifying approximation of constant Atherogenic Index value throughout life. The only approximation utilized is that a person retains, on the average, his *relative* ranking on the Atherogenic Index scale throughout life, an approximation that is known from other considerations to be quite valid. For purposes of estimation of coronary heart disease risk, if the 65 year old average man had accumulated his total amount in 35 years instead of 65 years, he would have had to show a much higher Atherogenic Index value throughout those 35 years. What Atherogenic Index would he have required to have accumulated this total amount in 35 years? Let us set this Atherogenic Index value as x units. From the trends in Atherogenic Index with age (Table XXIV), it can be stated that the Atherogenic Index value must have been 96% of x between 30 and 35 years, 88% of x between 25 and 30 years, 79% of x between 20 and 25 years, 73% of x between 15 and 20 years, 71% of x between 10 and 15 years, 70% of x between 5 and 10 years, and 70% of x between 0 and 5 years. The total accumulation by 35 years is to be 4,174 units. Therefore the *very simple* algebraic equation can be written:

$$5(0.96x) + 5(0.88x) + 5(0.79x) + 5(0.73x) + 5(0.71x) + 5(0.70x) + 5(0.70x) = 4174.$$

Solving for x, we obtain 152.3 units, which is the Atherogenic Index value at 35 years required to produce the same total accumulation in 35 years that the average 65 year old man accumulates in 65 years. From the risk table for 35 year old men (Table XV), an Atherogenic Index of 69.7 units corresponds to a relative risk of 3.77, whereas an Atherogenic Index of 152.3 units corresponds to a relative risk of 57.8. Therefore, on the accumulation basis, the average 65 year old man has a 57.8 over 3.77, or 15.3 fold higher risk of coronary heart disease than the average 35 year old man. The model described above for Atherogenic Index operating in an *accumulative* manner predicts, therefore, a 15.3 fold higher risk of coronary heart disease in the average 65 year old man than in the average 35 year old man, whereas the *instantaneous* operation had predicted nearly equal risks for these two men. Since the *observed* relative risk (from Vital Statistics) is 34.8 fold for 65 year old men versus 35 year old men, it is clear that the accumulative model brings us enormously closer to reality than does the instantaneous model.

However, this model so far only provides consideration of the Atherogenic Index factor. In Chapter V it was shown that the true risk for any individual of development of coronary heart disease from the known factors involved is arrived at by the *multiplication* of the risk from the blood pressure by the risk from the Atherogenic Index. Therefore it is now necessary to calculate the risk due to blood pressure as above and then to calculate the combined risks from blood pressure and from Atherogenic Index on the *accumulative* basis.

THE BLOOD PRESSURE CONSIDERED AS AN ACCUMULATIVE FACTOR

The procedure for calculation of coronary heart disease risk considering diastolic blood pressure to operate on an accumulative basis is entirely analogous to that for the Atherogenic Index. If the diastolic blood pressure operates in an accumulative fashion, then total accumulation toward risk is calculated by multiplying the diastolic blood pressure by the number of years during which that blood pressure has existed. The average blood pres-

sure trends with age from birth out to the eighth decade of life are available (Table XXV). Thus for the average 35 year old man with a diastolic blood pressure of 71.0 mm Hg, the average pressure between 30 and 35 years would have been 70.1 mm Hg, between 25 and 30 years, 68.3 mm Hg, between 20 and 25 years, 66.5 mm Hg, between 15 and 20 years, 63.7 mm Hg, between 10 and 15 years, 61.4 mm Hg, between 5 and 10 years, 60.5 mm Hg and between 0 and 5 years, 60.0 mm Hg. The total accumulation toward coronary disease risk for the average 35 year old man would, therefore, be 70.1x5 + 68.3x5 + 66.5x5 + 63.7x5 + 61.4x5 + 60.5x5 + 60.0x5, or 2,253 units in toto. The same type of arithmetic for the average 65 year old man yields a total accumulation of 4,482 units. If the 65 year old man were to have accumulated this total amount in 35 years instead of 65 years, he would have had to have had a much higher diastolic blood pressure at 35 years of age. What diastolic blood pressure would have been required? This is readily

TABLE XXV

DIASTOLIC BLOOD PRESSURE TRENDS WITH AGE FOR UNITED STATES MALES AND FEMALES

Age (in years)	*Diastolic Blood Pressure (in mm Hg)* *Males*	*Females*
Birth	(60.0)	(60.0)
5	60.0	(60.0)
10	60.9	60.0
15	61.9	61.0
20	65.5	63.5
25	67.5	63.9
30	69.2	64.6
35	71.0	65.5
40	72.6	68.1
45	74.0	70.5
50	74.7	74.6
55	75.5	75.3
60	75.8	77.7
65	76.0	79.8
70	75.8	81.8

Values in parenthesis are estimated from fewer than 25 cases. They are hence not stably fixed

calculated by the same methods utilized for the Atherogenic Index. The requisite blood pressure value may be designated as x mm Hg. From the age trends in diastolic blood pressure values (Table XXV) the blood pressure between 30 and 35 years of age would have been (0.99x) mm Hg, between 25 and 30 years, (0.96x) mm Hg, between 20 and 25 years, (0.94x) mm Hg, between 15 and 20 years, (0.90x) mm Hg, between 10 and 15 years, (0.86x) mm Hg, between 5 and 10 years, (0.85x) mm Hg, and between 0 and 5 years, (0.84x) mm Hg. The total accumulation toward risk must be set equal to 4,482 units Therefore, this simple algebraic equation holds:

$$(0.99x) \times 5 + (0.96x) \times 5 + (0.94x) \times 5 + (0.90x) \times 5 + (0.86x) \times 5 + (0.85x) \times 5 + (0.84x) \times 5 = 4482$$

Solving for x, we obtain 141 4 mm Hg as the diastolic blood pressure required for the average 65 year old man to have accumulated as much in 35 years as he does at his actual diastolic blood pressure in 65 years. From Table XIV relating blood pressure value to risk of coronary heart disease, it is seen that a blood pressure of 71.0 mm Hg corresponds to a risk of 2.25, whereas a blood pressure of 141.4 mm Hg corresponds to a risk of 11.8 Therefore, on the accumulative basis of operation of the blood pressure factor, the predicted risk for the average 65 year old man is 11.8 over 2.25, or 5.24 times that for the average 35 year old man. This is to be contrasted with the relative risk of 3.43 over 2.25, or 1 5 times, estimated for the diastolic blood pressure operating as an *instantaneous* factor. It is clear that the accumulative operation of blood pressure provides a relative risk estimate much more in accord with observational data (The Vital Statistics) than does instantaneous operation of the blood pressure

THE COMBINED RISK OF CORONARY HEART DISEASE WITH BOTH ATHEROGENIC INDEX AND DIASTOLIC BLOOD PRESSURE CONSIDERED AS ACCUMULATIVE FACTORS

Since the overall risk of coronary heart disease is obtained by multiplying the risk arising from the Atherogenic Index by that arising from the diastolic blood pressure, it is now appro-

priate to estimate this overall risk from the estimates for each of these factors operating in an accumulative manner. The Atherogenic Index, operating as an accumulative factor, leads to a predicted risk for 65 year old men 15.3 times that for 35 year old men. The diastolic blood pressure, operating as an accumulative factor, leads to a predicted risk for 65 year old men 5 24 times that for 35 year old men. Multiplying 15.3 by 5.24 yields a combined, or overall, risk for 65 year old men 80.2 times that for 35 year old men. Proceeding along similar lines, the expected comparison in fatal coronary heart disease rate for 45 and 55 year old men with that for 35 year old men can be calculated, with Atherogenic Index and blood pressure operating as accumulative factors. All these evaluations plus the observational information from Vital Statistics are presented in Table XXVI. These comparisons show that this first approximation to a model of accumulative operation of Atherogenic Index and diastolic blood pressure provides predicted ratios for one age group of men compared with another age group within a factor of 2 to 2.5 of the observed ratios from U. S. Vital Statistics This is to be contrasted with the gross inconsistency of being approximately a factor of 35 times away from observation when the two factors are considered to operate as instantaneous ones. Clearly, accumulative operation provides an answer enormously closer to reality The fact that accumulative operation is still approximately a factor of 2 or 2 5 off from observation is hardly dis-

TABLE XXVI

[illegible] TION [illegible] STATISTICS

(MALES)

Age Groups Under Comparison	*Predicted Ratio of Fatal Coronary Disease Attack Rates*	*Observed Ratio of Fatal Coronary Disease Attack Rates (U S Vital Statistics)*
65 years versus 35 years	80.2	34.8
55 years versus 35 years	34 9	13 4
45 years versus 35 years	9 4	4.1

calculated by the same methods utilized for the Atherogenic Index. The requisite blood pressure value may be designated as x mm Hg. From the age trends in diastolic blood pressure values (Table XXV) the blood pressure between 30 and 35 years of age would have been (0.99x) mm Hg, between 25 and 30 years, (0.96x) mm Hg, between 20 and 25 years, (0.94x) mm Hg, between 15 and 20 years, (0.90x) mm Hg, between 10 and 15 years, (0.86x) mm Hg, between 5 and 10 years, (0.85x) mm Hg, and between 0 and 5 years, (0.84x) mm Hg. The total accumulation toward risk must be set equal to 4,482 units. Therefore, this simple algebraic equation holds:

$$(0.99x) \times 5 + (0.96x) \times 5 + (0.94x) \times 5 + (0.90x) \times 5 + (0.86x) \times 5 + (0.85x) \times 5 + (0.84x) \times 5 = 4{,}482$$

Solving for x, we obtain 141.4 mm Hg as the diastolic blood pressure required for the average 65 year old man to have accumulated as much in 35 years as he does at his actual diastolic blood pressure in 65 years. From Table XIV relating blood pressure value to risk of coronary heart disease, it is seen that a blood pressure of 71.0 mm Hg corresponds to a risk of 2.25, whereas a blood pressure of 141.4 mm Hg corresponds to a risk of 11.8. Therefore, on the accumulative basis of operation of the blood pressure factor, the predicted risk for the average 65 year old man is 11.8 over 2.25, or 5.24 times that for the average 35 year old man. This is to be contrasted with the relative risk of 3.43 over 2.25, or 1.5 times, estimated for the diastolic blood pressure operating as an *instantaneous* factor. It is clear that the accumulative operation of blood pressure provides a relative risk estimate much more in accord with observational data (The Vital Statistics) than does instantaneous operation of the blood pressure.

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Since the overall risk of coronary heart disease is obtained by multiplying the risk arising from the Atherogenic Index by that arising from the diastolic blood pressure, it is now appro-

over a period of time in order to result in the accumulation of visibly evident lesions. In all the experimental animal studies which have been done over the years on the development of a lesion somewhat analogous to the human lesion of intimal arteriosclerosis, it has been noted that, where blood lipoprotein, or lipid, elevation is utilized to produce the lesion, the lesions do not develop instantaneously but rather require *time* to develop. Furthermore, the longer the lipoprotein elevation has existed the more extensive is the development of the lesions. Similarly, with respect to the blood pressure factor, the work of Heptinstall and co-workers showed clearly that, for a particular blood lipid elevation, the extent to which lesion development was aggravated by the existence of hypertension was greater the longer the period of maintenance of elevated blood pressure, cogent evidence for the accumulative operation of the blood pressure factor. It is important to repeat here that such pathological considerations are in no way being utilized as the prime basis for the accumulation concept. The general thesis rests upon its own merits specifically in connection with the problem of human coronary heart disease. It is reassuring to find the concept in excellent agreement with the human pathological and experimental animal evidence.

THE PRACTICAL CLINICAL IMPLICATIONS OF THE ACCUMULATIVE OPERATION OF ATHEROGENIC INDEX AND BLOOD PRESSURE IN CORONARY HEART DISEASE

Since the evidence is extremely strong that the Atherogenic Index and the blood pressure factors operate over a period of time to increase *the risk of future* clinical coronary heart disease, or to accumulate what may be referred to as additional *sub clinical* coronary heart disease, this evidence must be reckoned with in appraising the clinical approach to the patient. As an illustration, suppose that a group of 20-25 year old males is being evaluated as part of a general adult screening program for assessment of the risk of *future* clinical coronary heart disease. A small percentage of these 20-25 year old men will show

turbing, considering the several places in this first approximation to a model that can produce some error in prediction. It is likely that refinements both in the data available (including the U. S. Vital Statistics) and in the model itself may eliminate even the remaining discrepancy.

In problems such as this not only is it pertinent to examine whether accumulative versus instantaneous operation gives better consistency with actual observations with respect to one phenomenon (here, risks of fatal coronary heart disease) but also the evidence must be viewed in an over-all light with respect to reasonableness. There exists a large mass of additional information which argues strongly in favor of the accumulative mode of operation both of the Atherogenic Index and of the blood pressure rather than the instantaneous mode of operation. For example, there are the phenomena surrounding the difference in corornary heart disease incidence rate between men and women, phenomena which will be treated in extensive detail in the next chapter. However, it can be stated here that the only reasonable way in which the differences in heart attack rate between men and women can be explained in terms of the findings for *the Atherogenic Index and the blood pressure is via accumulative* operation rather than via instantaneous operation. To return to pathological consideration (although as repeatedly emphasized in this book no special support for the over-all concept is required from pathological considerations), two entities may be considered, first, xanthomatosis in humans and second, arteriosclerosis development in experimental animals. In families *demonstrating the lesion of xanthomatosis it is found* that some young members of these families show the same degree of lipoprotein elevation as do other members of the family, such as, for example, their parents The parents have fully developed, large xanthomatous lesions while the younger members in the family may have minimal lesions or none at all. Follow-up of this phenomenon by Piper and Orrlid[34] has shown that this is a matter of passage of time. If the younger members are followed over a period of time they do develop xanthomatous lesions This is direct evidence, for a lesion similar to that of arteriosclerosis, which indicates that high lipoprotein levels must *operate*

over a period of time in order to result in the accumulation of visibly evident lesions. In all the experimental animal studies which have been done over the years on the development of a lesion somewhat analogous to the human lesion of intimal arteriosclerosis, it has been noted that, where blood lipoprotein, or lipid, elevation is utilized to produce the lesion, the lesions do not develop instantaneously but rather require time to develop. Furthermore, the longer the lipoprotein elevation has existed the more extensive is the development of the lesions Similarly, with respect to the blood pressure factor, the work of Heptinstall and co-workers showed clearly that, for a particular blood lipid elevation, the extent to which lesion development was aggravated by the existence of hypertension was greater the longer the period of maintenance of elevated blood pressure, cogent evidence for the accumulative operation of the blood pressure factor. It is important to repeat here that such pathological considerations are in no way being utilized as the prime basis for the accumulation concept The general thesis rests upon its own merits specifically in connection with the problem of human coronary heart disease It is reassuring to find the concept in excellent agreement with the human pathological and experimental animal evidence

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extremely high Atherogenic Index values. Such Atherogenic Index values imply a risk of coronary heart disease for these men which is extremely high compared to that for those 20-25 year old men who have low Atherogenic Index values. Such relative risk may be in the neighborhood of 5, 10, 15, or 30 times as high for the men with very high Atherogenic Index values as for men with very low Atherogenic Index values. In spite of this, clinically the conclusion should not be drawn that these men are all going to expire immediately from coronary heart disease. For some strange reason certain workers who do not appear to understand the entire problem clearly seem to regard the fact that such men do *not* immediately drop dead of coronary heart disease as being in itself testimony adequate to refute the entire body of evidence concerning blood lipids and their relationship to coronary heart disease. Indeed precisely the opposite is the correct expectation. In spite of the marked elevation of the Atherogenic Index in such young individuals and of the fact that 30 men with high Atherogenic Index values will die of coronary heart disease in any specified time period for every one with a very low Atherogenic Index who dies of coronary heart disease in that same time period, it is still true that the vast majority of the 25 year old men with high Atherogenic Index values will be alive in one year, in five years, and even in ten years This is true simply because it takes a *certain amount of time* over which very high Atherogenic Index values must operate in order to increase the risk to a point where an appreciable proportion of the men are dying per year. Indeed reasonable estimates of this phenomenon have been made[39] to determine how many of these men will die each year of clinical coronary heart disease. Listed in Table XXVII is the proportion of an original group of 35 year old men that will be dead of coronary heart disease in 1, 5, 10, 15, 20 and 25 years for very low Atherogenic Index values and for very high Atherogenic Index values. Inspection of these data indicates that even for the very high Atherogenic Index value group, at the end of 1 year well over 95% of the men still survive. The entire concept predicts that this many will survive one year simply because they have not accumulated enough risk to have a higher death rate On the other hand,

TABLE XXVII

PERCENTAGE OF MEN ESCAPING FATAL CORONARY HEART DISEASE IN RELATION TO AGE AND ATHEROGENIC INDEX VALUES

(For Men whose Atherogenic Indices are Determined at 35 years of age)

Atherogenic Index at 35 years of age	*% Alive 1 Year Later*	*% Alive 5 Years Later*	*% Alive 10 Years Later*	*% Alive 15 Years Later*	*% Alive 20 Years Later*	*% Alive 25 Years Later*
20	99.998	99.99	99.98	99.97	99.94	99.92
40	99.997	99.98	99.97	99.85	99.55	99.2
60	99.996	99.92	99.68	99.1	97.9	96.2
80	99.98	99.73	99.0	97.3	94.8	91.1
100	99.85	98.95	97.2	89.2	81.9	70.5
120	99.75	98.1	95.1	89.4	80.9	66.3
140	99.5	96.6	91.1	81.2	65.6	42.0
160	99.3	93.9	83.0	66.8	43.9	Less than 18.0
180	98.8	91.2	77.6	52.1	23.3	Less than 5.0
200	98.5	86.8	64.3	32.3	6.4	Less than 1.0

this in no way is inconsistent with the prediction that hundreds of times as many of these men will have died even in one year as is found for the men with very low Atherogenic Index values. As the accumulation goes on with passage of years at the high Atherogenic Index values, the fraction of individuals who survive begins to drop off rather sharply, such that at 25 years beyond the original evaluation it is found that over 99% of the high group (A.I. = 200 units) is expected to be dead and that the death rate per year is high. However, for the low Atherogenic Index group even 25 years later less than 1% is expected to be dead, and the death *rate* per year is still comparatively low. The clinical maxim to be derived from this is that, for a person with a *very high Atherogenic Index* value at a young age, *the expectation* is *not* that he will very shortly be dead of clinical coronary heart disease Rather, the expectation is that he has a high chance of living for several years. On the other hand, it is known that he is *accumulating coronary heart disease risk* at a markedly excessive rate compared with a person with a low Atherogenic Index value and that preventive measures are clinically indicated in order to reduce the rate at which he is accumulating such risk.

The other clinical concern that the accumulation concept must develop in the physician is that, with a high value of the Atherogenic Index and/or the blood pressure, he has evidence of a high rate of development of sub-clinical coronary heart disease, or alternatively, a high rate of accumulation of risk of future *clinical coronary heart disease. Since this is an accumulative* process, the time most favorable for attempting to intercept a high rate of sub-clinical coronary heart disease development is as early as possible in the over-all development so as to prevent the actual accumulation of a high amount of sub-clinical coronary disease, or to prevent the accumulative establishment of a high risk of clinical coronary heart disease. Even if at some later time the rate of accumulation were lowered, this might be somewhat late. For even if the rate of accumulation is lowered at a particular point in later life, such that *new* risk is not accumulating at a rapid rate, the fact that a long period has passed at which such risk has been building up to make the total risk high can still result in a high coronary disease death rate for such indi-

viduals. The time for clinical action in this sphere is therefore early in adult life.

There is one possible consideration which might alter somewhat the clinical conclusions that would be arrived at from the model of an accumulative type of development of coronary heart disease risk. This is the all-important question of the extent to which a risk, once established, can be reversed by alteration of those factors which lead to the risk. With respect to coronary heart disease, assume that, as a result of an elevated blood pressure and an elevated Atherogenic Index over a period of years, a man has accumulated a high risk of coronary heart disease developing clinically at any particular time in the future. What is the possibility not only that his rate of accumulation of *new* risk will be altered if he should lower his blood pressure and his Atherogenic Index, but also that the risk already accumulated may itself decrease to some extent? Another way of asking this question is, "What is the prospect that, once a certain amount of sub-clinical coronary heart disease (regarding sub-clinical heart disease as the accumulation of risk of the later clinical event) has developed, some of this sub-clinical coronary heart disease is reversible?" The precise answer to this question is not available at this time. If some of the ancillary evidence is sought out, for example, that pertaining to the arteriosclerotic lesion and to the xanthomatotic lesion (a lesion which undoubtedly is closely related to that which leads to an accumulation of sub-clinical coronary heart disease and to the accumulation of clinical coronary heart disease risk), some highly suggestive clues are obtained. It is known that the arteriosclerotic lesion in experimental animals is definitely reversible to a large extent when the instigating factors are reduced in intensity. Thus where lipoprotein elevation in experimental animals leads to the accumulation of arterial lesions, it is known that not only do new lesions fail to develop when the lipoprotein levels are lowered, but also that some of the accumulated lesions do show reversal and diminution in size[40] In the author's own experience with human xanthomatotic patients, in every case where lesions were developing at an appreciable rate and where large established lesions were present during the time when lipoprotein levels were

high, two phenomena accompanied a lowering in lipoprotein levels. First, new lesions failed to develop and second, old lesions already established showed marked regression and, in many cases, complete disappearance. The older the lesion, the less chance there was for its complete disappearance when the lipoprotein-lowering regimen was instituted. These are illustrations showing that, for lesions associated with coronary heart disease, the reduction in intensity of factors which determine the rate of accumulation of the lesion not only had the effect of reducing the rate of *new* accumulation but also the effect of allowing reversal mechanisms to exceed development rates, with resulting regression of established lesions. Whether or not one should translate such evidence *directly* for the case of coronary heart disease risk is immaterial The precise, possible rate of any reversal of accumulated coronary disease risk cannot be evaluated at the present time, although efforts are being made to set up models and to test concepts in this direction. Until such evidence can be clearly crystallized, and until the exact extent to which reversal of any established risk of future clinical coronary heart disease can be mitigated by altering the current accumulation is known, it would certainly seem on the side of a clinical prudence to count very little on the reversal of already established risk. Every energy should therefore be centered upon the earliest possible lowering of the rate of accumulation of *new* risk. It should be obvious that, if one starts with 60 year old men to determine whether they have a high risk of coronary heart disease as a result of an elevation in Atherogenic Index and an elevation in blood pressure, they have had a very long period of years in which high levels may have operated and hence have contributed to an already-existing large risk of clinical coronary heart disease. Therefore, while it would certainly be reasonable to attempt to reduce the rate of accumulation of new risk in such men, it should also be expected that, even for a regimen which lowers the Atherogenic Index drastically and which lowers the blood pressure to a very satisfactory range, many such men will still go on to develop clinical and fatal coronary heart disease as a result of their *already-accumulated high risk*. If 50 year old men with the same Atherogenic Index and blood pressure values

are considered, the outlook is more favorable, since they have had ten fewer years in which to accumulate risk due to these high values. It would be clinically very helpful to apply preventive medicine for 50 year old men rather than for 60 year old men Extension of such reasoning makes it quite obvious that if men have already identified themselves at least with respect to one of these factors, the Atherogenic Index, by the time they are in their twenties, the ideal time to start lowering the risk of clinical coronary heart disease, precisely because of the age-related accumulative character of coronary disease risk, is at that time. The age-related accumulative character of coronary disease risk underlines the real place for medicine to attack the problem of coronary heart disease To be sure, *established* clinical coronary heart disease must be treated in any particular patient who already has this disease for he is justifiably primarily concerned about established clinical coronary heart disease. However, more rewarding clinical results can be expected from the treatment of a person *before* he becomes a patient with overt coronary heart disease. In few medical problems does the evidence argue more strikingly in favor of a preventive approach rather than a therapeutic approach to the disease than it does in the case of coronary heart disease This will require a considerable re-orientation in the thinking of the physician and of the public with respect to *who* is a patient. Patients of real importance with respect to clinical coronary heart disease are not patients with established disease but rather the entire adult population of the United States Since there exists no simple way to know without actually making the determinations who the persons are with elevated blood pressures or elevated Atherogenic Index values, or both, and who hence are accumulating coronary heart disease risk at the most rapid rate, it will be essential to consider as patients, or potential patients, every adult in the population

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Statistics to confirm these major differences in heart attack frequency for men as compared with women. Every physician is well aware of this difference, and indeed, as mentioned above, some have thought the differences even much larger than those which really exist In the experience of many physicians the occurrence of documentable clinical coronary heart disease in the form, for example, of myocardial infarction in a woman below the age of 40 years is so rare that the initial impression of some physicians is to discount the possibility of this diagnosis except under certain special circumstances Coronary heart disease can and does occur in women even at young ages but it is indeed relatively infrequent as compared with its incidence in men. Where do we go with this type of information? Obviously when a dramatic feature of a disease such as coronary heart disease reveals itself, such as by showing a major sex difference in incidence, there exists the possibility that an understanding of the basis for this sex difference may lead to great clarification in understanding over-all aspects of the disease process itself. In consideration of the male-female difference in coronary heart disease incidence and its possible basis, let us outline the salient features which observational material has provided. These are as follows

1. Early in adult life the incidence of clinical coronary heart disease and fatality therefrom is approximately four or five times in men compared with women.

2 There is a progressive decrease in this ratio of attacks, fatalities, and incidence of clinical coronary heart disease between men and women with advancing years, such that in approximately the eighth decade the incidence rate approaches equality

3 The incidence of hypertension as a factor in the development of clinical coronary heart disease seems to be distinctly more prominent in the female sex than in the male (see Chapter IV).

4 The incidence of diabetes mellitus as a factor in predisposing women to heart attacks seems to be greater than that in men

All of these salient points concerning the differences in coro-

Chapter VIII

THE DIFFERENCE BETWEEN MEN AND WOMEN WITH RESPECT TO CORONARY HEART DISEASE

MEN IN THE United States unquestionably have a higher frequency of manifestations of coronary heart disease, clinical and fatal, then do women. No single fact concerning the occurrence of coronary heart attacks is more striking to the physician viewing this over-all problem. To some extent the difference between men and women with respect to coronary heart disease incidence has been exaggerated in several sources, possibly due to bias in the type of material observed. However, the data available through the United States Vital Statistics concerning the comparative heart attack rates for men and women clearly indicate that at least for relatively youthful groups the frequency of such heart disease in men greatly exceeds that in women, with that difference *shrinking progressively with increasing age.* These data were presented in Table XXIII. Not only do the data presented there indicate that men, on the average, have a greater incidence rate of coronary heart disease than do women at several ages, but certain other tremendously striking features of this difference emerge. Whereas in the age decade from 30-39 years the incidence of fatal clinical coronary heart disease is some 4.5 times in men that which occurs in women, with each passing decade the difference between men and women shrinks so that by the time the seventh decade of life is reached the incidence rate in men is approximately 2 3 times that for the women. That these differences are real for the population in the United States and for the present era is beyond question There is certainly no further proof or evidence required beyond the U. S. Vital

value and that which obtains from the blood pressure value. Therefore it will be necessary to consider not one but both of these factors in determining the risk differences between men and women at various ages

THE BLOOD LIPOPROTEIN (ATHEROGENIC INDEX) FACTOR IN MEN AND WOMEN

Measurements for the S_f0-12, 12-20, 20-100, 100-400 lipoprotein classes and the derived Atherogenic Index values are available for men and women at ages up to 70 years of age. Such information is presented in Table XXVIII for these lipoprotein classes. The Atherogenic Index data are in Table XXIV. Certain facts are clear Whereas the lipoprotein levels are not strikingly different in early life[41], there is a sharp divergence in blood lipoprotein levels between the sexes in the teens and in the twenties, with the males showing higher values of all four important classes of lipoproteins and of the Atherogenic Index than do the females Whereas the males show steep rises in level of the various lipoprotein classes during the third decade of life, the females, on the average, lag behind although there is a slow rise in lipoprotein levels At a somewhat later age when the men are levelling out in average value for the various lipoprotein classes and even showing declining values, the women are showing a marked increase in values, until finally for each lipoprotein class there is reached an age, differing somewhat for the various lipoprotein classes, at which the average level in women becomes equal to the average level in men After that age the average lipoprotein level in women is higher than the average level in men For the Atherogenic Index, which summarizes all the lipoprotein information with respect to coronary heart disease, the age at which the average woman reaches the Atherogenic Index possessed by the average man is 64.5 years Thereafter women show, on the average, higher Atherogenic Index values than do men, at least out to the eighth decade of life. Inspection of the data reveals further that the major differences between the male and the female sex are in the lipoprotein classes of high flotation rate, namely, in the S_f12-20, in the S_f20-100, and

nary heart disease between men and women deserve careful evaluation for whatever leads they may provide with respect to the over-all genesis of coronary heart disease. Possible explanations for these major observations which surround the difference between coronary heart attack rate in men and women fall into two possible categories; (1) The differences observed can be explained on the basis of those factors already known and established to be associated with coronary heart disease, namely the level of certain important lipoprotein classes in the blood (expressed as the composite value, the Atherogenic Index) or the level of the diastolic blood pressure, or both. Or, (2) Certain wholly new and independent factors which have not as yet been evaluated are operative.

The proper approach to this problem scientifically is to determine *first* whether or not either known factor, the lipoprotein levels or the blood pressure, explains the described male-female difference in all its manifestations completely or in part If these major known factors explain the difference *completely*, then there is no reason whatever to go on to the second possibility, namely the search for unknown, untested, unheard of additional factors, since there would be nothing for such factors to explain. Any such search would then be fruitless and a waste of time It is axiomatic in science for this type of problem that, when certain known factors of independent merit associated with a disease exist and when a new observation arises for consideration, one tests whether the new observation is truly new or whether it can be explained by operation of the existing known factors. Any other approach to such a problem is certainly not sound scientific methodology, for it essentially negates the existence of all knowledge already developed. Therefore, the primary step in this evaluation is a determination of whether or not the lipoprotein factor, or the blood pressure factor, or a combination of these two explains any part or all of the difference in male-female incidence of coronary heart disease If such factors do *not* explain the differences observed, it would then be *necessary* to go on to other possible explanations. Total risk of coronary disease arising from established factors is best expressed by multiplication of the risk that obtains from the Atherogenic Index

value and that which obtains from the blood pressure value. Therefore it will be necessary to consider not one but both of these factors in determining the risk differences between men and women at various ages

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TABLE XXVIII

Age Trends for the Various Lipoprotein Classes in United States Males and Females*

Lipoprotein Classes

Age** (years)	Mean S_f 0-12 mg/100ml		Mean S_f 12-20 mg/100ml		Mean S_f 20-100 mg/100ml		Mean S_f 100-400 mg/100ml	
	Males	Females	Males	Females	Males	Females	Males	Females
20	300.0	276.0	30.0	28.0	62.9	41.1	28.0	6.7
25	319.0	293.0	38.7	32.5	73.1	46.9	36.2	9.3
30	338.3	310.5	45.8	31.9	83.0	52.5	41.3	11.8
35	357.0	326.5	51.6	41.1	92.9	58.1	52.4	14.0
40	372.0	338.7	55.1	45.2	101.8	61.3	60.7	16.3
45	381.0	319.6	57.2	48.5	109.1	70.6	67.6	18.9
50	389.0	358.0	57.3	51.3	110.9	77.3	63.6	21.8
55	383.5	361.5	56.2	53.5	103.5	81.3	57.8	21.7
60	373.6	369.2	54.2	55.8	91.3	91.0	50.0	27.3
65	363.5	372.7	52.0	57.9	79.2	97.1	41.8	29.5
70	353.3	375.0	49.7	59.7	68.0	101.9	33.8	31.5

* Recent mean values for lipoprotein levels in women above 30 years, especially of S_f 20-400 classes, are lower than earlier published values. The recent values are for employed women at the University of California (Livermore), whereas published values are primarily for women in Framingham. A "best" value is reported here between the two sets. Framingham women have appreciably higher relative weights than do the recently studied employed women.

** Data for lipoprotein levels below 20 years of age are based upon a small series of cases and are hence not reproduced here. See reference 41 for approximate values.

very strikingly in the S_f100-400 lipoproteins. From the lower Atherogenic Index values maintained in the youthful years of adult life by the average woman as compared with the average man and from the fact that the entire distribution of values in women as compared with men is shifted toward lower values, it can be immediately predicted that the heart attack rate should be lower in the female sex during the young adult years than it is in the male sex. The next question to consider is *how much* lower it is predicted to be. In a previous chapter, it was shown that the most consistent explanation of the relationship of coronary heart disease risk with Atherogenic Index and blood pressure require that these factors both operate in an *accumulative* manner rather than as instantaneous factors. Therefore in analysis of this problem concerning the male-female difference in coronary heart disease incidence we may treat the Atherogenic Index values in the male and female on the accumulative basis to determine how much of the excessive risk which characterizes the male sex is thereby explained. At 35 years of age the men show a coronary heart disease incidence rate approximately 4.5 times that of women (U.S. Vital Statistics). In Chapter VII it was demonstrated, by consideration of successive five year age intervals, that the average 35 year old man has accumulated 1903 units toward his risk of coronary heart disease, that is for the portion of total risk which arises via the Atherogenic Index value. A calculation of the number of units accumulated by the average female during the first thirty-five years of life proceeds along precisely similar lines. For the average female the trends in Atherogenic Index values with age are such that between 30 and 35 years the Atherogenic Index value is 50.4 units, at 25 to 30 years, it is 46.7 units, at 20 to 25 years, it is 42.8 units, at 15 to 20 years, it is 40.7 units, at 10 to 15 years, it is 40.3 units, at 5 to 10 years, it is 40 units, and between 0 and 5 years, it is 40 units. Therefore, the total accumulation for the average woman at 35 years of age is expressed in the following, simple algebraic equation,

$$\text{Total accumulation} = 5 \times 50.4 + 5 \times 46.7 + 5 \times 42.8 + 5 \times 40.7 + 5 \times 50.3 + 5 \times 40.0 + 5 \times 40.0 = 1505 \text{ units}$$

Now to compare the average female with the average male at 35 years in terms of coronary heart disease risk it is necessary

to determine what Atherogenic Index a 35 year old man would have to have if he were to have accumulated 1505 units by 35 years (which is what the above calculation shows that the average *woman has accumulated in her first 35 years of life*). We may set this required Atherogenic Index value for a 35 year old male at x units and then solve for x. From the trend of Atherogenic Index with age for men, it is known that between 30 and 35 years, such a man would have had an Atherogenic Index value = 96% of x, between 25 and 30 years, 88% of x, between 20 and 25 years, 79% of x, between 15 and 20 years, 73% of x, between 10 and 15 years, 71% of x, between 5 and 10 years, 70% of x, and between 0 to 5 years, 70% of x.

The total accumulation = 5x (0.96 (x)) + 5x (0.88 (x)) + 5x (0.79 (x)) + 5x (0.73 (x)) + 5x (0.71 (x)) + 5x (0.70 (x)) + 5x (0.70 (x))

But this total accumulation is being set equal to 1505 units Solving for x yields 54.9 units, which is the Atherogenic Index value a man would have to have at age 35 years to have accumulated as much as has the *average* woman by age 35 years. From Table XV it is now possible to determine how the coronary heart disease risk for this Atherogenic Index value, 54.9 units, compares with the risk for an Atherogenic Index of 69.7 units (which is the average value for men at 35 years. The two relative risks are 2.20 and 3.77 Therefore, with accumulative operation of the Atherogenic Index, the risk tables predict that the average 35 year old man has 3.77 over 2.20, or 1.71 times the *cornary heart disease risk of the average 35 year old woman.* There is a more refined method for calculating the relative risk of 35 year old men versus 35 year old women, based upon calculation of average risk directly instead of the risk of the person with the average Atherogenic Index value. However such a refined calculation does not materially alter the relative risk for 35 year old men versus 35 year old women obtained above. Thus, Atherogenic Index alone, operating as an accumulative factor, leads to the expectation of a 1.71 fold coronary heart disease risk in men of 35 years as compared with women 35 years of age. But this accounts only for the effect of one of the major known factors determining the risk of coronary heart disease. The other factor, the blood pressure, must be evaluated

before the overall prediction can be compared with observational *data*.

THE CONTRIBUTION OF THE BLOOD PRESSURE EFFECT TO THE DIFFERENCE IN CORONARY HEART DISEASE INCIDENCE BETWEEN MEN AND WOMEN

The contribution of the diastolic blood pressure to the difference in coronary heart disease risk between 35 year old men and women proceeds along lines similar to those for the Atherogenic Index contribution, with the diastolic blood pressure to be considered as an accumulative factor. The average blood pressure trends for men from birth out to late age are available in Table XXV. For the average 35 year old man the diastolic blood pressure is 71.0 mm Hg. The average 35 year old woman has a diastolic blood pressure of 65.3 mm Hg. From the trend of blood pressure with age for the female sex, it can be estimated that between 30 and 35 years this woman had a diastolic pressure of 65.0 mm Hg, between 25 and 30 years, 64.2 mm Hg, between 20 and 25 years, 63.7 mm Hg, between 15 and 20 years, 62.2 mm Hg, between 10 and 15 years, 60.5 mm Hg, between 5 and 10 years, 60.0 mm Hg, between 0 and 5 years, 60.0 mm Hg. Therefore, for this average 35 year old woman the total accumulation toward coronary heart disease risk from diastolic pressure as an accumulative factor = 5x65.0 + 5x64.2 + 5x63.7 + 5x62.2 + 5x60.5 + 5x60.0 + 5x60.0 or = 2178 units. In order to use the Table for relative risk of coronary heart disease versus diastolic pressure (which is based upon data for men) it is necessary now to calculate what diastolic pressure a man would have to have at 35 years if he is to have accumulated as many total units (2178) during 35 years as have been accumulated by the average 35 year old woman. Let x be the value of this required diastolic blood pressure. Then between 30 and 35 years, such a man's pressure would be 0.99 x, between 25 and 30 years, 0.96 x, between 20 and 25 years, 0.94 x, between 15 and 20 years, 0.90 x, between 10 and 15 years, 0.86 x, between 5 and 10 years, 0.85 x, and between 0 and 5 years, 0.84 x. The total accumulation by 35 years of age would be:

$$5(0.99\,x) + 5(0.96\,x) + 5(0.94\,x) + 5(0.90\,x) + 5(0.86\,x) + 5(0.85\,x) + 5(0.84\,x)$$

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The total accumulation = 5x (0.96 (x)) + 5x (0.88 (x)) + 5x (0.79 (x)) + 5x (0.73 (x)) + 5x (0.71 (x)) + 5x (0.70 (x)) + 5x (0.70 (x))

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culated for 45 year olds, for 55 year olds, and for 65 year olds These predictions and their comparison with the observational data from U.S. Vital Statistics are presented in Table XXIX. The agreement based upon the accumulation model can be considered excellent It has been proposed that a difference in the thickness of the intimal lining of the coronary arteries may be a factor helping to account for the male-female difference in coronary heart disease incidence but no real development of any significance has come from this proposal. Another factor proposed concerns the so-called susceptibility of the coronary arteries to the deposition of lipids, the postulation being made that such susceptibility is under the influence of estrogenic hormone. Again this highly speculative proposal has no evidence which appears to substantiate it. Undoubtedly other factors will be and have been proposed At the present time, such factors are speculative and without any distinct evidence to support them.

TABLE XXIX

COMPARISON OF FATAL CORONARY HEART DISEASE INCIDENCE RATE FOR MEN VERSUS WOMEN ESTIMATED FROM ATHEROGENIC INDEX PLUS DIASTOLIC BLOOD PRESSURE WITH OBSERVATIONAL DATA FROM U. S. VITAL STATISTICS

Age Group (years)	*Predicted Ratio of Fatal Coronary Heart Disease (Men/Women)*	*Observed Ratio of Fatal Coronary Heart Disease Rate (Men/Women)*
35	2.10	4.45
45	2.72	3.85
55	2.74	3.20
65	2.62	2.26

THE BASIS FOR THE HIGHER [illegible] TENSION IN WOMEN [illegible] DISEASE IN COMPA[illegible] CORONA[illegible] DISEASE

In Chapter IV it was pointed out that nearly every reported study in the literature shows elevation in blood pressure to be a more frequent occurrence in the women who develop coronary

But this is to be set equal to the total accumulation for the average 35 year old woman, which is 2178 units.

Therefore 31.7x = 2178 or x = 68.7 mm Hg, which is the diastolic pressure required at 35 years for the man who has accumulated from diastolic blood pressure as much toward coronary heart disease risk as has the average 35 year old woman. This man is to be compared with the average 35 year old man. For a diastolic pressure of 68.7 mm Hg, the relative risk of coronary heart disease (from Table XIV) is 1.83 x that for the reference value of 50 mm Hg, whereas for a diastolic pressure of 71.0 mm Hg, such relative risk is 2.25 x that for the reference value of 50 mm. Therefore the average man of 35 years has 2.25 over 1.83 = 1.23 times the risk of coronary heart disease that a 35 year old man with a diastolic blood pressure of 68.7 mm. However, this latter man was a "calculated" man to provide the same accumulative value from diastolic pressure that characterizes the average 35 year old woman. Therefore diastolic blood pressure alone, operating as an accumulative factor, leads to a prediction that the average 35 year old man should show 1.23 times the risk of future clinical coronary heart disease that the average 35 year old woman shows.

THE COMBINED EFFECT OF THE DIASTOLIC BLOOD PRESSURE AND ATHEROGENIC INDEX OPERATING AS ACCUMULATIVE FACTORS IN CORONARY HEART DISEASE IN MEN AND WOMEN

From the Atherogenic Index alone the relative risk for the average 35 year old man compared with the average 35 year old woman is 1.71 times as high, and from the blood pressure the relative risk for the man compared with the woman is 1.23 times as high. As developed in Chapter V, the best approximation to *overall risk* of coronary heart disease is obtained by multiplication of the risk from Atherogenic Index by that from diastolic blood pressure. Therefore the overall risk for the 35 year old man is calculated to be 1.71x1 23, or 2.10 times that for the average 35 year old woman. By entirely similar methods the predicted coronary disease risk for men versus women may be cal-

The overall coronary heart disease risk was then determined for each person in the usual manner, namely *multiplication* of the risk from Atherogenic Index by that from blood pressure. These overall coronary heart disease risks were then ranked from the highest to the lowest, in separate lists for the men and the women For convenience each group of 100 persons can be subdivided into ten risk categories, each containing ten persons, and the median risk for each category calculated for the ten persons in that category. Such data are presented in Table XXX, ranked from the lowest risk category to the highest for each sex. Now our 100 men and 100 women are each sub-divided into 10 subgroups, for each sub-group the median risk being known and the distribution of blood pressures being known. Suppose now that a very large population sample of 50-59 year old persons were studied during a period when they are overtly healthy. In a person of time of observation de novo clinical coronary heart disease will develop in each of the 10 sub-categories of overall risk, *the number* of cases in each category being directly pro-

TABLE XXX

RANKING OF 50-59 YEAR OLD MEN AND WOMEN UPON MEDIAN CORONARY DISEASE RISK
(10 Categories for Each Sex)

	MEN Median Risk* (setting lowest category = 1.00)	*WOMEN* Median Risk* (setting lowest category = 1.00)
Lowest Category of 10	1.00	1.00
2nd " "	2.35	1.88
3rd " "	2.77	2.09
4th " "	3.19	2.61
5th " "	4.23	2.94
6th " "	6.23	4.00
7th " "	9.31	4.58
8th " "	13.08	5.85
9th " "	18.65	8.64
Highest " "	50.96	16.94

* Relative risks were calculated from the [illegible]

heart disease at a particular age than in the men who do so. So marked has been this difference in some series that the authors had erroneously concluded that hypertension is not a factor in the development of coronary heart disease in men but is a major factor in its development in women. Hypertension has been conclusively shown to be a major factor in the development of coronary heart disease *both* in men and women. Indeed there exists no reason to believe there is any lack of equivalence of a particular degree of blood pressure elevation with respect to acceleration of sub-clinical coronary heart disease development in men versus women. Why, then, should hypertension be a more frequent finding in women who experience clinical coronary heart disease than in men who develop that disease? Fortunately, there now exists sufficient quantitative information concerning the factors which determine the risk of clinical coronary heart disease in men and women to provide the answer to this highly important question.

From the relationship of coronary heart disease incidence rate with Atherogenic Index and diastolic blood pressure, it should be possible to *calculate* whether or not hypertension should be a *more frequent finding in coronary heart disease among women* than among men. This calculation is, additionally, illustrative of some of the uses of risk data and is presented in detail. A random sample of 100 men and 100 women in the age decade, 50-59 years, from a larger sample of the population study at Framingham, Massachusetts, was selected for this analysis. For each person the Atherogenic Index and the diastolic blood pressure were available. Therefore, for each person the risk of future coronary heart disease can be estimated, utilizing the appropriate risk tables (Table XIV and Table XVI). Before using the risk versus Atherogenic Index table for 50-59 year men to calculate the risks for the women, the equivalent Atherogenic Index for men to accumulate by 55 years the same total number of units accumulated by a woman with a particular Atherogenic Index value had to be determined This was described in detail in Chapter VII. Then both for the 100 men and the 100 women the coronary heart disease risk arising from Atherogenic Index and from diastolic blood pressures were calculated separately.

the lowest risk category. Now for each category the total number of cases, and the number in each category with diastolic pressures above 110 mm Hg are as follows;

Lowest category, 100 total cases, of which 0 have pressures above 110 mm Hg.
2nd category, 188 total cases, of which 0 have pressures above 110 mm Hg
3rd category, 209 total cases, of which 0 have pressures above 110 mm Hg
4th category, 261 total cases, of which 0 have pressures above 110 mm Hg
[illegible]

The total number of de novo cases of coronary disease in women is obtained by adding those in each category, yielding 5053 cases. Of these 953 will be characterized by pressures above 110 mm Hg This represents 18 9% of the total group Therefore, all these calculations lead to the conclusion that 18.9 over 11.2, or *1 7 times* as many women of 50-59 years of age developing coronary heart disease would have shown pre-coronary pressures above 110 mm Hg as would men of 50-59 years of age who develop coronary heart disease. Utilizing a blood pressure of 120 mm Hg, it is calculated that 16 0% of women who develop coronary heart disease would have shown diastolic blood pressures above 120 mm Hg, whereas only 0 4% of men of the same age group who develop coronary disease would have shown pressures above 120 mm Hg. The direction of the effect and the general order of magnitude of the increase in frequency of hypertension in coronary disease in women versus men, predicted from Atherogenic Index-Blood Pressure risk estimates, is therefore in accord with observational experience. Precise estimation of the difference would, of course, be better obtained by the study of much larger population samples Thus, while the very calculation itself takes cognizance of the importance of blood pressure as a risk factor *for both sexes,* the *concept still* provides consistency with the observational experience that hypertension is a more *frequent* accompaniment of coronary heart disease in women than in men Qualitatively this could have been anticipated from the fact that men and women are more nearly alike up to 55 years of age in blood pressure than in Atherogenic Index. Hence

portional to its risk. Thus, if for the men, we wait until 100 cases of de novo coronary disease arise out of the *lowest category*, the data of Table XXX inform us that, in the same time interval there will be the following number of de novo coronary heart disease cases in the other nine categories:

If lowest category develops 100 cases, then;

2nd category develops	235 cases
3rd category develops	277 cases
4th category develops	319 cases
5th category develops	423 cases
6th category develops	623 cases
7th category develops	931 cases
8th category develops	1,308 cases
9th category develops	1,865 cases
10th category develops	5,096 cases

The total number of cases of de novo coronary heart disease is obtained by adding all the cases together, yielding 11, 177. From the distribution of blood pressure values of the 100 sample men age 50-59 years in each sub-category, the *fraction* of each sub-category with blood pressures above any particular value is immediately known. We may calculate, for example, the number of cases of de novo coronary disease in each sub-category with pressures above 110 mm Hg by multiplying this fraction by the number of cases in the category

Therefore, we can estimate that there will be,

of 100 cases in category 1,	0 above 110 mm Hg
of 235 cases in category 2	0 above 110 mm Hg
of 277 cases in category 3	0 above 110 mm Hg
of 319 cases in category 4,	0 above 110 mm Hg
of 423 cases in category 5,	42 above 110 mm Hg
of 623 cases in category 6,	0 above 110 mm Hg
of 931 cases in category 7,	186 above 110 mm Hg
of 1308 cases in category 8	0 above 110 mm Hg
of 1865 cases in category 9,	0 above 110 mm Hg
of 5096 cases in category 10,	1019 above 110 mm Hg

The total number of de novo coronary disease cases with pressures above 110 mm Hg is 42 + 186 + 1019, or 1247 cases. Therefore, of the 11,177 de novo coronary disease cases in men 11.2% have pressures above 110 mm Hg. Proceeding along similar lines for the women, we can consider a time period long enough for 100 cases of de novo coronary disease to develop in

Chapter IX

THE RELATIONSHIP OF OVERWEIGHT WITH CORONARY HEART DISEASE

In today's medical practice there are few features more associated in the physician's mind with excessive cardiovascular disease in general, and with coronary heart disease in particular, than the phenomenon of overweight. Indeed some physicians have interpreted essentially all the recent dietary work relating to coronary heart disease as being associated with caloric intake and the phenomenon of overweight. While this latter view is incorrect, it does underline the fact that overweight is high in the minds of physicians as a factor predisposing to cardio-vascular disease It is therefore, pertinent to determine precisely to what extent overweight is related to coronary heart disease and then to determine what mechanism may operate to make for an association between overweight and coronary heart disease, assuming such association to exist. This last point is most crucial, for according to current day practice a large number of physicians feel that an overweight patient should reduce in *weight* in the effort to minimize his chances for development of future coronary heart disease. This implies that simply *being* overweight is regarded by the physician as the factor which is responsible for any excessive risk of coronary heart disease. It implies furthermore that there is nothing that can be done to delineate among the overweight individuals those who are especially prone to develop heart disease from those who may have even a lower risk of coronary heart disease than many underweight individuals Therefore, mechanism by which overweight may become associated with coronary heart disease is an issue of paramount importance, once the exact extent of the association is established.

blood pressure would be expected to contribute a greater share of the risk of coronary disease in women than in men, and therefore hypertension should be more prominent in women. The mathematics formalizes this qualitative estimate.

THE ROLE OF ESTROGENIC HORMONES

The large difference in coronary heart disease mortality rate among young women and young men and the finding of markedly lower lipoprotein levels in young women as compared with young men, (a difference which decreases with increasing age) has naturally prompted great interest in the question of whether or not both the difference in disease incidence and in lipoprotein levels might be related to something about estrogenic hormone production in the female compared with the male. The effects of estrogenic hormones upon serum lipoprotein levels have been, and continue to be, extensively studied. Such studies do indeed indicate that pharmacologic estrogenic hormones can profoundly influence serum lipoprotein levels, although they do not provide any evidence concerning physiologic estrogen production or handling as the basis for lipoprotein levels being different in men and women The pharmacologic effects of estrogens upon serum lipoproteins and Atherogenic Index will be discussed in detail in Chapter XV.

The last question concerning differences in coronary heart disease incidence between men and women relates to the findings in diabetes mellitus Since this question is but part of the broader question of coronary heart disease in diabetes mellitus in general, this will be treated in Chapter XII

Chapter IX

THE RELATIONSHIP OF OVERWEIGHT WITH CORONARY HEART DISEASE

IN TODAY'S medical practice there are few features more associated in the physician's mind with excessive cardiovascular disease in general, and with coronary heart disease in particular, than the phenomenon of overweight. Indeed some physicians have interpreted essentially all the recent dietary work relating to coronary heart disease as being associated with caloric intake and the phenomenon of overweight. While this latter view is incorrect, it does underline the fact that overweight is high in the minds of physicians as a factor predisposing to cardio-vascular disease It is therefore, pertinent to determine precisely to what extent overweight is related to coronary heart disease and then to determine what mechanism may operate to make for an association between overweight and coronary heart disease, assuming such association to exist This last point is most crucial, for according to current day practice a large number of physicians feel that an overweight patient should reduce in *weight* in the effort to minimize his chances for development of future coronary heart disease This implies that simply *being* overweight is regarded by the physician as the factor which is responsible for any excessive risk of coronary heart disease. It implies furthermore that there is nothing that can be done to delineate among the overweight individuals those who are especially prone to develop heart disease from those who may have even a *lower* risk of coronary heart disease than many underweight individuals Therefore, mechanism by which overweight may become associated with coronary heart disease is an issue of paramount importance, once the exact extent of the association is established.

First of all, it must be stated that the association between overweight and coronary heart disease is far from perfect. Every physician who practices medicine realizes fully that many, many patients with coronary heart disease are not overweight, that patients develop coronary heart disease and die from it with weights considered within the normal, or usual, range, and furthermore that many patients develop coronary heart disease and die from it who are underweight by our usual height-weight standards. Such considerations would still be correct even after adjusting for such possibilities as difference in body frame and an incorrect appraisal of the exact amount of true adipose tissue in a particular patient. With all such adjustments it would still be apparent that many people who are underweight or at normal *weights can and do develop coronary heart disease. Furthermore*, even though overweight may be a factor associated with excessive coronary heart disease, many overweight patients remain so for many years without developing any signs and symptoms of coronary heart disease. Where then does the evidence come from which leads to so much emphasis on overweight as a factor in degenerative vascular disease and, in particular, as a factor in the development of coronary heart disease? Probably the single most valid source of evidence on this subject is that which derives from the studies of life insurance policyholders These studies were in the nature of a follow-up of insured policyholders at varying degrees of overweight and underweight, from those who were markedly overweight to those who were well below the ideal weight for their height and build Such studies were reported by Dublin[42], the statistician for the Metropolitan Life Insurance Corporation Individuals were accepted for policies who were overweight, but were rated upward in premium because of their status of overweight The exact analysis of Dublin's findings relating the coronary heart disease incidence rate in such policyholders to degree of overweight are presented in Table XXXI It is quite clear from the data presented there that among Dublin's insured policyholders who were 35% overweight the incidence of coronary heart disease was approximately 50% above that in the population of individuals who were at or below ideal weight. This difference is large, it is highly significant,

and is essentially irrefutable. To the author's knowledge no one has published any evidence which would contradict the findings of Dublin on these insured policyholders with respect to the excessive predisposition of appreciably overweight individuals to the development of fatal coronary heart disease. Yet in a variety of ways some investigators have attempted to cast doubt upon this solidly established and highly significant information which has been published by Dublin concerning the relationship of overweight and coronary heart disease. Many who have cast doubt upon this relationship have utilized studies of the extent of overweight in patients with already-established clinical coronary heart disease in comparison with persons free of such manifest disease. For example, Gertler and White[30] in their study of 97 men who developed myocardial infarction below the age of 40 years contrasted with a group of matched controls of the same age but without evidence of myocardial infarction were unimpressed with the difference in the degree of overweight of their myocardial infarction patients and their control series. There is every reason to study the phenomenon of overweight in a series of patients with established clinical coronary heart disease, such as survivors of myocardial infarction, and to contrast the find-

TABLE XXXI

MORTALITY FOR PERSONS RATED UP IN INSURANCE PREMIUMS FOR OVERWEIGHT

(Age group 20-64 years)

(from Dublin)

% Departure from Average Weight (all cases overweight)	*Mortality (Expressed in % of Deaths Relative to Persons of Normal Weight)* MEN %	WOMEN %
Less than 30%	142	139
30 39%	151	148
40 49%	178	156
50 59%	234	175
60 74%	282	145

For all classes of overweight ... that for per ...

ings in such a series with those in a series of individuals who have not developed clinical coronary heart disease. In this text analogous data have been presented in previous chapters concerning lipoprotein findings. However, it has been pointed out carefully in previous discussions here that there are some major pitfalls that can deceive the unwary investigator in the use of such clinical material. The crucial issue concerning overweight is the extent to which individuals who are overweight go on to develop clinical coronary heart disease *in the future.* This is essentially the type of study for which Dublin has provided us with information. On the other hand, studies of clinical coronary heart disease already established in the form of survivorship of myocardial infarction are performed on a population of individuals who have not only developed clinical coronary heart disease but *who have been cared for by physicians.* The extremely long history of medical suspicion of the unfavorable aspects of being overweight is such that overweight patients being treated for acute myocardial infarction are almost certain to lose weight during the period of hospitalization for the acute myocardial infarction. Additionally, many of them are encouraged to lose weight and do lose weight during the period of recovery from myocardial infarction. A large number of such individuals will indicate upon questioning that their weight is considerably below the usual weight that had characterized them during the 5, 10, 15 or 20 years which had preceded their myocardial infarction. On the other hand, many such patients hardly know what their body weight had been before their myocardial infarction. When asked whether they have altered their diet as a result of their myocardial infarction, they will deny that they have, and yet when records are withdrawn detailing previous medical examinations, insurance examinations, or employment examinations, it has been noted repeatedly that their post-myocardial infarction weight is considerably below their pre-myocardial infarction weight. This is not to say that a certain number of patients may not gain weight after myocardial infarction as a result of the lesser physical activity allowed them in the course of their medical advice, but one can be certain that the danger exists, in the study of such clinical material as survivors of myocardial

infarction, of an appreciable loss of weight in many patients. Certainly one should be very wary of accepting data on the body weight of post-myocardial infarction patients as being of real consequence with respect to the average degree of overweight in healthy individuals who will subsequently go on to develop myocardial infarction. Undoubtedly Gertler and White were well aware of the possible biassing which this factor would have introduced into their study. Hence, while it is worthwhile knowing what their findings are, reliance on such evidence to provide us with any evidence of a relationship between overweight and the incidence of myocardial infarction is hardly indicated. The same type of criticism should be levelled at a variety of other studies in the literature that have purported to show that the average survivor of myocardial infarction does not show any appreciable degree of overweight in comparison with the average person who has not experienced a myocardial infarction. There does exist now in the literature another clear-cut study of the appropriate type concerning the relationship of overweight with development of clinical coronary heart disease, that is, heart disease occurring *after* the determination of the person's *weight status*. It is only from such prospective studies of individuals whose weight is known in advance and who are subsequently followed that a valid determination can be made of the extent to which overweight predisposes to clinical coronary heart disease. This latter study was conducted by the National Heart Institute of the United States Public Health Service in the community of Framingham, Massachusetts, as part of a long-term survey of the development of cardiovascular disease and other diseases in individuals of a reasonably representative community in the United States. These data have been recently published[23]. In that study 52 acceptable, documented cases of "arteriosclerotic heart disease" were observed to develop over a 4 year period out of a population sample of 898 men who had undergone complete physical examinations. Analyses of the data showed clearly that the attack rate of coronary heart disease was appreciably and significantly greater during the four-year follow-up period for the overweight men than for otherwise comparable, but not

ings in such a series with those in a series of individuals who have not developed clinical coronary heart disease. In this text analogous data have been presented in previous chapters concerning lipoprotein findings. However, it has been pointed out carefully in previous discussions here that there are some major pitfalls that can deceive the unwary investigator in the use of such clinical material. The crucial issue concerning overweight is the extent to which individuals who are overweight go on to develop clinical coronary heart disease *in the future*. This is essentially the type of study for which Dublin has provided us with information On the other hand, studies of clinical coronary heart disease already established in the form of survivorship of myocardial infarction are performed on a population of individuals who have not only developed clinical coronary heart disease but *who have been cared for by physicians*. The extremely long history of medical suspicion of the unfavorable aspects of being overweight is such that overweight patients being treated for acute myocardial infarction are almost certain to lose weight during the period of hospitalization for the acute myocardial infarction. Additionally, many of them are encouraged to lose weight and do lose weight during the period of recovery from myocardial infarction. A large number of such individuals will indicate upon questioning that their weight is considerably below the usual weight that had characterized them during the 5, 10, 15 or 20 years which had preceded their myocardial infarction On the other hand, many such patients hardly know what their body weight had been before their myocardial infarction. When asked whether they have altered their diet as a result of their myocardial infarction, they will deny that they have, and yet when records are withdrawn detailing previous medical examinations, insurance examinations, or employment examinations, it has been noted repeatedly that their post-myocardial infarction weight is considerably below their pre-myocardial infarction weight. This is not to say that a certain number of patients may not gain weight after myocardial infarction as a result of the lesser physical activity allowed them in the course of their medical advice, but one can be certain that the danger exists, in the study of such clinical material as survivors of myocardial

relationship either of blood lipoproteins or blood pressure with overweight might increase the hazard of overweight persons of developing future clinical coronary heart disease, it would be pertinent to know whether there is or is not there is still left over any extra hazard of coronary heart disease in overweight persons If there is *no* extra hazard left over to be accounted for, the notion that the phenomenon of overweight per se increases the hazard of coronary disease could be dispelled. If there *is* an extra hazard left over, it is urgent to learn the nature of its possible basis.

OVERWEIGHT, LIPOPROTEIN LEVELS, AND ATHEROGENIC INDEX VALUES

The evidence discussed above clearly implicates overweight as a factor producing an excessive risk of clinical coronary heart disease, and hence, correspondingly, an excessive rate of development of sub-clinical coronary heart disease. The extent to which this effect of overweight can be explained by any possible association of overweight with the blood level of the four important lipoprotein classes (S_f0-12, S_f12-20, S_f20-100 and S_f100-400) and with the derived value, the Atherogenic Index, must be understood Population samples are available for whom the blood lipoproteins, height, and weight have been measured as a routine part of periodic employment examinations so that a reasonable cross section of individuals of both sexes and at various ages is available for study of this issue. The measured values of the various lipoprotein classes and of the combined value which summarizes the information with respect to coronary heart disease, namely the Atherogenic Index, are listed for various degrees of overweight in Table XXXII. In these tabulations degree of overweight or underweight is expressed in terms of the value known as the "relative weight" of an individual The definition of relative weight, as used here, is the person's actual body weight divided by the "ideal body weight," utilizing the Metropolitan Life Insurance Height and Weight Tables to determine ideal weight Thus, if an individual is characterized by relative weight of 1 20, it is meant that his weight is 20% above

overweight, men. The actual findings reported by Dawber and co-workers in the Framingham Study were as follows:

Weight Category	Attack Rate of "Arteriosclerotic Heart Disease" in New Cases Per 1000 at Risk (4 year period)
20% or more above median weight	123 cases per 1000
13 to 19% above median weight	105 cases per 1000
0 to 12% above median weight	50 cases per 1000
Below median weight	40 cases per 1000

The evidence derived from this study indicates an association of overweight with heart disease risk of approximately the same order of magnitude as that previously published by Dublin. There existed every reason to expect that these data would confirm Dublin's data, and they do In the face of such strong evidence from both the study of Dublin on the insured overweights and the data of the Framingham Heart Project there would appear less reason than ever to question the positive relationship of overweight with the subsequent development of clinical coronary heart disease. Rather the strong evidence should make even more suspect conclusions concerning overweight derived from the study of myocardial infarction survivors

With the clear-cut establishment of an association of overweight with excessive coronary heart disease risk, several questions come to the fore. First, the evidence derived in previous chapters demonstrated two major features characterize individuals in terms of their subsequent risk of clinical coronary heart disease. These are: (1) their blood lipoprotein levels and atherogenic index values, and (2) their habitual blood pressures It is pertinent, first, to determine the extent to which overweight may influence either of these two factors. For, if either the lipoprotein level and atherogenic index value are elevated on the average in overweight individuals, or if the blood pressure is elevated on the average in overweight individuals, there would exist a well-defined basis for the expectation of a positive association between overweight and the hazard of clinical coronary heart disease. Of even greater importance, some insight into the mechanism by which such association arises would be available. Once an estimate were available of the extent to which a

the ideal weight listed by the Metropolitan Height and Weight Tables No need exists to claim that the "ideal" values listed in the Metropolitan Life Insurance Tables are truly ideal weights. They do serve as a set of useful reference points, and any findings based upon their use would hardly be altered in any significant manner by any other choice of reference weights

All four lipoprotein classes (S_f12, 12-20, 20-100, and 100-400) and the Atherogenic Index show appreciable rises in average value upon comparison of the significantly underweight individuals with those appreciably overweight, with a fairly smooth rising trend for the intermediary weight groups. Inspection of the table for various individual lipoprotein classes reveals that the effect of overweight is more strikingly associated with elevation of the S_f20-100 and S_f100-400 lipoproteins than it is with elevation of the S_f0-12 and S_f12-20 lipoproteins. At the outset, it must be stressed that these variations in lipoprotein levels and Atherogenic Index values with degree of overweight are *average* findings for the group of individuals in each particular relative weight range In any particular relative weight range, individuals are found who have low, moderate, or even quite high Atherogenic Index values, although there will be a *higher frequency* of high values of the Atherogenic Index with a higher degree of overweight than with a moderate degree of overweight, and correspondingly a higher frequency of high values with a moderate degree of overweight than for groups markedly below ideal weight Similarly there exists a higher frequency of low values in individuals who are underweight or at ideal weight in comparison with those who are appreciably overweight. These findings all occur because the correlation between relative weight and Atherogenic Index is far from perfect even though it is clear-cut and definite This point is summarized in Table XXXIII, which gives the frequency of various Atherogenic Index values at various degrees of overweight and underweight, in a study group of 834 men in the 30-39 year age category. The entire group of men is then divided into four sub-groups, those 10% or more underweight, those between 10% underweight and 10% overweight, and those 10 to 20% overweight, and those 30% or more overweight (all on the relative weight scale). In each

TABLE XXXII

Relationship of Degree of Overweight with Blood Lipoprotein Levels and Atherogenic Index Values

(Based upon study of 834 consecutive 30-39 year old men)*

Relative Weight Group	Number of Cases	Mean Lipoprotein Level (mg/100ml) S_f0-12	S_f12-20	S_f20-100	S_f100-400	Mean Atherogenic Index (units)
Less than 0 80 (Mean = 0 76)	11	347 2	56 9	78 6	36 3	61.9
0 80 0 89 (Mean = 0 86)	86	337 8	11.4	70 1	33.2	59.1
0 90 0 99 (Mean = 0 95)	219	319 2	18 2	83 1	38.5	61 6
1 00-1 09 (Mean = 1 05)	219	355 3	51 3	91 6	48 8	69.1
1 10 1 19 (Mean = 1 11)	168	367 1	55 3	100 4	61.1	75 2
1 20 1 29 (Mean = 1 23)	75	360 9	51 9	112 9	78.1	79.1
1 30 or higher (Mean = 1 37)	26	369 2	55 3	116 0	86 7	82 0

* All men were employees at one industrial installation. Examinations were part of periodic medical examinations

coronary heart disease for individuals of several ages at various Atherogenic Index values. Thus, if illustrative considerations are limited to 30-39 year old males, those tabulations will allow a ranking of individuals upon the Atherogenic Index values and a direct calculation of the relative incidence rate of clinical coronary heart disease at one Atherogenic Index value for comparison with the incidence rate at any other Atherogenic Index value. The data of Table XXXII indicate that for 30-39 year old males the individual who is 35% overweight will show an average Atherogenic Index value of approximately 82 units, whereas the individual who is at ideal weight will show an average Atherogenic Index value of 67 units. From Table XV for the value of 82 Atherogenic Index units (in those individuals 35% overweight) the risk of coronary heart disease would be 7.0 times the reference value of 30 A I. units, and for individuals at ideal weight whose Atherogenic Index value is 67 units, the risk of coronary heart disease would be 3.4 times the reference value. Therefore, the relative risk or rate of mortality from coronary heart disease for these two groups would be the first value divided by the second, or a 7 0 over 3.4 = 2.1 fold increase in attack rate for the overweight group compared with the ideal weight group. The first approximation has been obtained by calculating the risk of coronary heart disease for the average person who is 35% overweight Therefore Atherogenic Index *elevation in* overweight persons leads to a prediction of excessive *coronary heart* disease mortality between the published values of Dublin and of Dawber. However, overall coronary disease risk requires evaluation of the contribution from the blood pressure as well as from the Atherogenic Index

RELATIONSHIP OF OVERWEIGHT, BLOOD PRESSURE, AND CORONARY HEART DISEASE

The evaluation of a feature such as overweight in relation to excessive coronary heart disease would be incomplete without an analysis of the extent to which overweight may affect blood pressure, and to which this may alter coronary heart disease incidence rate There have been numerous studies of the relation-

TABLE XXXIII

Distribution of Atherogenic Index Values in the Various Relative Weight Categories

(30-39 year old men)

Relative Weight Category	*Atherogenic Index Values* "Low" Less than 60 (units)	"Moderate" 60-89 (units)	"Elevated" 90-109 (units)	"Markedly Elevated" 110 or higher (units)
Less than 0.90	53.8%	41.2%	1.7%	3.4%
0.90-1.09	38.9%	45.4%	10.6%	5.0%
1.10-1.29	26.0%	51.1%	12.7%	10.2%
Greater than 1.30	26.4%	38.2%	20.6%	14.7%

such category the fraction of the group with markedly elevated, elevated, moderate, and low Atherogenic Index values are presented. It is seen that any value of the Atherogenic Index *can* occur in any of the relative weight categories, but clearly the high values are *more frequent* in the overweight groups than in the other groups. Correspondingly, low Atherogenic Index values are more frequent in the underweight groups than in the other weight categories.

EXTENT TO WHICH THE ATHEROGENIC INDEX ELEVATION IN OVERWEIGHT INDIVIDUALS ACCOUNTS FOR THEIR INCREASED CORONARY HEART DISEASE MORTALITY

Dublin's data on insured overweights demonstrated that the 35% overweight individual shows approximately a 1.5-fold mortality from diseases of the coronary arteries compared with the individual who is at ideal weight. Dawber's Framingham data indicate approximately a 3-fold mortality for the same degree of overweight. In the effort to understand the mechanism for this observed increase in mortality, the extent to which the effect of overweight on factors known to be associated with coronary heart disease might be expected to alter the mortality from coronary heart disease must be determined. In Chapter V were presented the tabulations which give the incidence rate for clinical

is given the relative risk (of coronary heart disease or coronary heart disease incidence rate) for various diastolic blood pressure values: For a diastolic pressure of 78.7 mm Hg the coronary heart disease risk is 3.9. For a diastolic pressure of 74.7 mm Hg the coronary heart disease risk is 3.2. Therefore the relative coronary heart disease rate for the average person 35% overweight (whose mean pressure is 78.7 mm Hg) is 1.2 fold that of the average person at ideal weight, (whose mean pressure is 74.7 mm Hg). This is the extent to which the degree of overweight increases coronary heart disease risk via the association of the former with the diastolic blood pressure.

THE COMBINED EFFECT OF ATHEROGENIC INDEX AND BLOOD PRESSURE ELEVATION IN INCREASED RISK OF CORONARY HEART DISEASE IN OVERWEIGHT PERSONS

It was demonstrated earlier (see Chapter V) that the Atherogenic Index and the diastolic blood pressure are independent factors operating to determine the risk of coronary heart disease in any individual. Further, it was shown that the best approximation to the overall risk of coronary heart disease from these two independent factors can be estimated by multiplication of the coronary disease risk factor for the Atherogenic Index effect by that for the diastolic blood pressure. In this case, for the comparison of the average person who is 35% overweight with the average person at ideal weight the Atherogenic Index increases the coronary heart disease risk 2.1 fold, and the diastolic blood pressure increases that risk 1.2 fold. The combined effect of both factors therefore predicts a 2.1x1.2, or 2.5 fold coronary heart disease risk (or incidence rate) for the 35% overweight individual. This lies between the 1.5 fold risk reported by Dublin and the 3 fold risk reported by Dawber. Certainly it would appear that the major effect of overweight in production of an increase in coronary heart disease risk is explainable through the combination of its effects upon the Atherogenic Index and the diastolic blood pressure. There may well exist no excessive risk

*The average of the pressure recorded by the physician (non-reclining) and that taken by the nurse (after 10 minute rest) is used here

ship between overweight and blood pressure[43, 44, 45]. The measured relationship between blood pressure and relative weights for the 30-39 year old men described above is presented in Table XXXIV. The regular progression of increasing average diastolic blood pressure with increasing average degree of overweight is apparent in the data of all investigators. Again, as with the Atherogenic Index, the finding of increase in diastolic blood pressure with increase in weight is an *average* trend. Therefore, at low relative weight, average weight, or at a marked degree of overweight, the diastolic blood pressure can be low, moderate, or high. But unmistakably there is an increasing frequency of high values of the diastolic blood pressure with increasing relative weight. From the data of Table XXXIV, the average diastolic blood pressure for 30-39 year old males 35% overweight is 78 7 mm Hg* in contrast with a pressure of 74 7 mm Hg for persons of the same age group who are at ideal weight. In Table XIV

TABLE XXXIV

RELATIONSHIP OF DEGREE OF OVERWEIGHT WITH DIASTOLIC BLOOD PRESSURE

(Based upon study of 834 consecutive 30-39 year old men)

Relative Weight Group	*Number of Cases*	*Mean Diastolic Blood Pressure (mm Hg)* NURSE*	PHYSICIAN**
Less than 0 80 (Mean = 0 76)	11	68 0	75.8
0.80-0.89 (Mean = 0 86)	86	69.1	76.9
0 90-0 99 (Mean = 0.95)	219	70 7	79.2
1 00-1 09 (Mean = 1.05)	249	69.5	79 1
1 10-1.19 (Mean = 1 14)	168	70.2	82 1
1.20-1.29 (Mean = 1.23)	75	71.1	84 6
1.30 or higher (Mean = 1.37)	26	71 8	85 9

* These blood pressures were taken by a nurse after 10 minutes of rest by the subject.
** These pressures were taken by the physician during the course of the physical examination, which preceded the rest period

is given the relative risk (of coronary heart disease or coronary heart disease incidence rate) for various diastolic blood pressure values: For a diastolic pressure of 78.7 mm Hg the coronary heart disease risk is 3.9. For a diastolic pressure of 74.7 mm Hg the coronary heart disease risk is 3.2. Therefore the relative coronary heart disease rate for the average person 35% overweight (whose mean pressure is 78.7 mm Hg) is 1.2 fold that of the average person at ideal weight, (whose mean pressure is 74.7 mm Hg). This is the extent to which the degree of overweight increases coronary heart disease risk via the association of the former with the diastolic blood pressure

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It was demonstrated earlier (see Chapter V) that the Atherogenic Index and the diastolic blood pressure are independent factors operating to determine the risk of coronary heart disease in any individual. Further, it was shown that the best approximation to the overall risk of coronary heart disease from these *two independent* factors can be *estimated* by multiplication of the coronary disease risk factor for the Atherogenic Index effect by that for the diastolic blood pressure. In this case, for the comparison of the average person who is 35% overweight with the average person at ideal weight the Atherogenic Index increases the coronary heart *disease risk* 2.1 *fold*, and the diastolic blood pressure increases that risk 1 2 fold. The combined effect of both factors therefore predicts a 2.1x1.2, or 2.5 fold coronary heart disease risk (or incidence rate) for the 35% overweight individual This lies between the 1.5 fold risk reported by Dublin and the 3 fold risk reported by Dawber. Certainly it would appear that the major *effect of overweight* in production of an increase in coronary heart disease risk is explainable through the combination of its effects upon the Atherogenic Index and the diastolic blood pressure. There may well exist *no* excessive risk

*The average of the pressure recorded by the physician (non-reclining) and that taken by the nurse (after 10 minute rest) is used here.

left over to be accounted for by *overweight per se.* Indeed there never did exist any direct evidence to indicate that load or strain upon the heart due to the phenomenon of overweight *per se* is in any way related to an increased risk of coronary heart disease. The semi-popular "excess baggage" concept of the effect of overweight upon the heart, at least with respect to coronary heart disease, finds no support from these data nor from any other scientific data.

THE PRACTICAL CLINICAL IMPLICATIONS OF THE MECHANISMS BY WHICH OVERWEIGHT INCREASES CORONARY HEART DISEASE RISK

That at least the major share of the effect of overweight in increasing the risk of coronary heart disease operates via the Atherogenic Index and blood pressure effects is hardly a matter of academic importance alone. Clinically, physicians have in general warned the overweight patient that his risk of coronary heart disease is increased by his status of being overweight. In an overall sense this has been completely correct However, now that at least the largest part of the mechanism by which overweight operates to produce an excessive coronary heart disease risk is understood, such a clinical approach is definitely outmoded. For, if an overweight person is one of the many who have "escaped" the effect of overweight upon Atherogenic Index and blood pressure level, then there exists no justification for assignment of an excessive coronary disease risk to that patient Instead such a patient can be re-assured that he does not share the *average* increase in coronary heart disease risk experienced by the overweight group It follows, also, that *some* overweight persons must experience a much greater-than-average effect of overweight upon either the Atherogenic Index or the diastolic blood pressure or both. *Such persons are subject to a much* greater increase in coronary heart disease risk as a direct result of their being overweight than is the case for the "average" person overweight to the same extent. It becomes apparent, then, that clinically much more can be done to assess the true significance of overweight in a particular patient when the blood

pressure and lipoprotein-Atherogenic Index measurements are available to the physician.

THE EFFECT OF CORRECTION OF OVERWEIGHT UPON ATHEROGENIC INDEX AND BLOOD PRESSURE VALUES

An important question arises in the mind of the clinician whenever a relationship between two physiological or biochemical variables has been demonstrated to exist That question is, "If one of the variables is changed in a favorable direction, will the other variable also change in a favorable direction?" This is certainly a valid question, for it is possible for two variables to be correlated, and yet to have one such variable uninfluenced when a *change* occurs in the other of the pair. In the present case, the problem centers around whether or not lipoprotein-Atherogenic Index values and blood pressure values will fall if overweight is corrected It is possible to conceive that some hypothetical third factor controls the degree of overweight and separately controls the Atherogenic Index value The observed correlation between overweight and Atherogenic Index value could, under these circumstances, be the result of a correlation of both of them with the hypothetical third factor. It can be imagined that correction of overweight might fail to alter the hypothetical third factor and hence fail to alter the Atherogenic Index value. Clearly, such speculation should well be replaced by a direct determination of what happens to lipoprotein-Atherogenic Index values and blood pressure when body weight is altered, both in the direction of an increase and a decrease.

There exist two ways of obtaining direct experimental answers to these questions in human subjects. One method involves the specific experiment of having a group of subjects diet to reduce in weight, with observation serially of Atherogenic Index and blood pressure changes. The other approach involves what may be properly regarded as a "natural experiment," in which individuals are observed over a period of years without any specific medical advice. Of their own choice some will eat more, others the same, and still others, less. Some will increase their physical activity, otheres will not change such activity, and

some will decrease their physical activity. The net result will be that some will increase in weight, others will remain unchanged, and still others will lose weight in such a natural experiment. The changes in a variable, such as Atherogenic Index, can readily be ascertained if such a group of persons is periodically checked as part of a routine examination without any knowledge of the nature of the experiment. Extensive data are now available for both types of experimental approach to the question of the effect of change in weight. Of the two types of data, those derived from the natural experiment are in many ways far more satisfactory to the physician in practise. His real interest lies in knowing what happens to persons altering their weights under the usual circumstances of living. Such natural experiments involve less of the drastic, unphysiologic, and unusual type of dietary regimen, and hence provide information more representative of the dietary patterns persons are likely to adhere to over long periods of time.

The data for such a natural experiment were obtained from serial blood studies of 374 men who were examined on two occasions, one to three years apart, in routine employment medical examinations Weight and lipoprotein levels were determined on both occasions, although none of the persons examined had any idea that such studies were in progress. Therefore it is hardly conceivable that factors such as an effort to lose weight rapidly before a medical visit could have operated to any significant extent in these studies. The subjects were considered on the basis of whether they had lost 5 or more pounds from the first to the second examination, lost 0 to 5 pounds, experienced no change, had gained 0 to 5 pounds, or had gained more than 5 pounds. Lipoproteins of the S_f0-12, 12-20, 20-100 and 100-400 classes plus the derived Atherogenic Index values were measured for all groups of subjects. The average changes for the several groups are presented in Table XXXV. It is clear from those data that the lipoproteins and Atherogenic Index values rise appreciably with increase in weight between the two examinations and that they fall appreciably for those men who decrease in weight between the two examinations This settles definitively the question concerning whether weight alteration does alter lipoproteins

TABLE XXXV

Effect of Weight Alterations on Serum Lipoprotein Levels and Atherogenic Index Values

("Natural" Experiment Involving 374 Subjects)

	Number of Subjects	Mean S_f0-12	Mean S_f12-20	Mean S_f20-100	Mean S_f100-400	Mean A.I.	Body Weight (pounds)
Persons Losing 5 or More Pounds Between Examinations							
1st Examination	73	351.7	50.6	99.5	61.6	71.9	180.6
2nd Examination	73	333.6	46.8	86.3	41.9	64.6	169.9
Change		− 18.1	− 3.8	− 13.2	− 19.7	− 7.3	− 10.7
Persons Losing 0 to 5 Pounds Between Examinations							
1st Examination	77	369.5	47.9	87.2	56.6	70.0	169.7
2nd Examination	77	358.4	50.7	91.8	53.8	69.7	167.6
Change		− 11.1	+ 2.6	+ 7.6	− 2.8	− 0.3	− 2.1
Persons Who Did Not Change in Weight Between Examinations							
1st Examination	37	350.3	41.1	81.4	45.1	63.9	165.6
2nd Examination	37	342.6	41.3	84.2	45.6	64.3	165.6
Change		− 7.7	+ 0.2	+ 2.8	+ 0.5	+ 0.4	0
Persons Who Gained 0 to 5 Pounds Between Examinations							
1st Examination	81	345.2	46.3	84.7	43.4	65.2	161.9
2nd Examination	81	352.1	50.0	96.6	60.5	72.1	164.3
Change		+ 6.9	+ 3.7	+ 11.9	+ 17.1	+ 6.9	+ 2.4
Persons Who Gained 5 or More Pounds Between Examinations							
1st Examination	103	355.7	52.2	93.2	49.3	69.5	162.3
2nd Examination	103	360.7	56.2	110.8	68.5	77.6	171.9
Change		+ 5.0	+ 4.0	+ 17.6	+ 19.2	+ 8.1	+ 9.6

some will decrease their physical activity. The net result will be that some will increase in weight, others will remain unchanged, and still others will lose weight in such a natural experiment The changes in a variable, such as Atherogenic Index, can readily be ascertained if such a group of persons is periodically checked as part of a routine examination without any knowledge of the nature of the experiment. Extensive data are now available for both types of experimental approach to the question of the effect of change in weight. Of the two types of data, those derived from the natural experiment are in many ways far more satisfactory to the physician in practise. His real interest lies in knowing what happens to persons altering their weights under the usual circumstances of living. Such natural experiments involve less of the drastic, unphysiologic, and unusual type of dietary regimen, and hence provide information more representative of the dietary patterns persons are likely to adhere to over long periods of time.

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Effect of Weight Alterations on Serum Lipoprotein Levels and Atherogenic Index Values

('Natural' Experiment Involving 374 Subjects)

	Number of Subjects	Mean S_f 0-12	Mean S_f 12-20	Mean S_f 20-100	Mean S_f 100-400	Mean A.I.	Body Weight (pounds)
Persons Losing 5 or More Pounds Between Examinations							
1st Examination	73	351.7	50.6	99.5	61.6	71.9	180.6
2nd Examination	73	336.6	46.8	80.3	41.9	64.6	169.9
Change		− 18.1	− 3.8	− 19.2	− 19.7	− 7.3	− 10.7
Persons Losing 0 to 5 Pounds Between Examinations							
1st Examination	77	369.5	47.9	87.2	56.6	70.0	169.7
2nd Examination	77	358.4	50.7	91.8	53.8	69.7	167.6
Change		− 11.1	+ 2.6	+ 7.6	− 2.8	− 0.3	− 2.1
Persons Who Did Not Change in Weight Between Examinations							
1st Examination	37	350.3	41.1	81.1	15.1	63.9	163.6
2nd Examination	37	342.6	41.3	81.2	15.6	64.3	163.6
Change		− 7.7	+ 0.2	+ 2.8	+ 0.5	+ 0.4	0
Persons Who Gained 0 to 5 Pounds Between Examinations							
1st Examination	84	345.2	46.3	84.7	43.4	65.2	161.9
2nd Examination	84	352.1	50.0	96.6	60.5	72.1	164.3
Change		+ 6.9	+ 3.7	+ 11.9	+ 17.1	+ 6.9	+ 2.4
Persons Who Gained 5 or More Pounds Between Examinations							
1st Examination	103	355.7	52.2	93.2	49.3	69.5	162.3
2nd Examination	103	360.7	56.2	110.8	68.5	77.6	171.9
Change		+ 5.0	+ 4.0	+ 17.6	+ 19.2	+ 8.1	+ 9.6

and Atherogenic Index values in the expected direction. The fact that lipoproteins and Atherogenic Index values *are* altered in the expected direction removes any need for a hypothetical third factor which controls body weight and lipoproteins independently. From the clinical point of view, weight reduction can be counted on to reduce lipoprotein-Atherogenic Index values, a favorable trend, whereas weight gain will result in a rise in Atherogenic Index values, a highly unfavorable trend.

The findings from the above-described natural experiment are supported by relatively short term experiments in overweight persons who were induced to lose weight on a prescribed 1000 calorie reduction diet, low in animal fat and in carbohydrate[46]. Twenty-eight women, all significantly overweight, participated in a weight reduction program over a two month period The lipoprotein and Atherogenic Index changes in this study are presented in Table XXXVI. Appreciable falls in all four classes of lipoproteins (S_f0-12, 12-20, 20-100, and 100-400) and in the Atherogenic Index values accompanied the weight loss which averaged 14 pounds for the overall group of 28 women. The probable mechanism by which weight reduction results in lipoprotein lowering, and weight gain, in lipoprotein elevation, are to be discussed in detail in Chapter X. The pertinent issue here is that both in short term medical studies and in long-term natural experiments, weight alterations are paralleled by lipoprotein and Atherogenic Index alterations.

CHANGES IN DIASTOLIC BLOOD PRESSURE WITH CHANGE IN WEIGHT

Precisely the same type of question arises with respect to the relationship of diastolic blood pressure to degree of overweight as arose for the Atherogenic Index-overweight relationship. Will correction of overweight result in a fall in the average diastolic blood pressure? The work of numerous investigators has established satisfactorily[47, 48, 49, 50, 51] that correction of overweight is attended by a fall both in systolic and diastolic blood pressures and that such reductions occur both in originally normotensive and hypertensive persons.

TABLE XXXVI

EFFECT OF SHORT-TERM MEDICAL WEIGHT REDUCTION PROGRAM OF SERUM LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES

(1000 calorie diet in 28 Female subjects)

	S_f0-12 mg/100ml	S_f12-20 mg/100ml	S_f20-100 mg/100ml	S_f100-400 mg/100ml	Atherogenic Index	Body Weight (pounds)
Initial Mean Values	372	93	91	61	81	212
Mean Values after 2 Months on Diet	326	61	72	27	61	198
Changes	− 46	− 32	− 22	− 37	− 20	− 14

EFFECT OF CORRECTION OF OVERWEIGHT UPON CORONARY HEART DISEASE MORTALITY

Both major factors known to be associated with increase in the risk of coronary heart disease mortality, the Atherogenic Index value and the diastolic blood pressure, are positively associated with the degree of overweight. Indeed these two factors together account for essentially all of the known effect of overweight in increasing the incidence rate, or risk, of coronary heart disease. Further, excellent evidence is available that correction of overweight will, on the average, alter the blood pressure factor and the Atherogenic Index in a favorable direction. This would lead to the expectation that correction of overweight should lead to a reduction in the incidence rate, or risk, of coronary heart disease. There already exists cogent, direct evidence to indicate that correction of overweight does, indeed, reduce the risk of fatal coronary heart disease. Dublin and Marks[52], of the Metropolitan Life Insurance Company, have reported on the mortality experience of persons originally rated up in insurance premiums because of overweight but who subsequently received lower ratings after reduction in weight This mortality experience was compared with that for the overall group of persons originally rated up in insurance premium for overweight For their entire group of cases they found for intermediate degrees of overweight a 42% increase in mortality in comparison with persons not rated up in premium, whereas for the group originally rated up but later rerated because of loss of weight the increase in mortality was only 13%. This is a marked reduction in mortality, and it is not even possible to prove that the 13% increase that remained was real For the extreme overweights they found a 79% increase in mortality for the overall group rated up, but for those who were re-rated because of loss in weight the increased mortality was only 9%, which again cannot definitely be proven to be a real increase. Unquestionably this evidence shows that overweight correction does reduce mortality risk. Since coronary heart disease is a major contributor to the excessive mortality observed, it is certain that this particular source of mortality was reduced. Thus not only do all the logical ele-

ments point to the expectation that correction of overweight will reduce the risk of coronary heart disease mortality, but the direct field test provides convincing evidence that this expectation is realized.

Chapter X

DIET AND CORONARY HEART DISEASE

No SUBJECT has been more in the limelight of possible approaches to coronary heart disease prevention and treatment than that concerning diet. From numerous sources and from a variety of types of information have come the suggestion that the diet which people habitually consume may in some way be related to their risk of premature coronary heart disease. It will be necessary to consider the validity of evidence concerning possible relationships between diet and coronary heart disease so as to facilitate the physician's decision concerning the practical application of diet in the prevention of coronary heart disease. Prominent among the types of evidence which bear upon this question have been those which associate a high incidence rate of coronary heart disease with prosperity in a country adequate to allow for abundant consumption of certain kinds of foods. Thus the Bantus of South Africa, the Okinawans, the Chinese, and the Japanese (at least during some era) have all been quoted to have a low incidence rate of coronary heart disease, whereas the population of countries of much greater prosperity and a higher food intake, not only of fat but also of calories in general, have been quoted to show a higher incidence rate of coronary heart disease As evidence that deserves careful perusal, such evidence is extremely valuable, for it may provide some major leads toward understanding of coronary heart disease However, among other criticisms, one criticism has been semi-justifiably levelled at such evidence in a serious way. That criticism has essentially stated the following: "If any two of the population groups quoted as having grossly different coronary disease death rates and grossly different diets are compared, it is found that a

wide variety of features can also be used to differentiate these populations beside that of diet."

First, it has been pointed out that the differences in climate and other aspects of the environment for the persons in one country as compared with those for persons in another country are as large, or larger, than the differences in habitual dietary intake of certain foods. Second, there are ethnic differences between the peoples of the various countries involved that might conceivably be associated with alterations as important as, or more important than the difference in food intake. Third, there are gross differences in major occupational activities for the individuals in some of these areas versus those in other areas. Occupation has on other grounds been singled out as a factor involved in the development of coronary heart disease (see Chapter XIV). Fourth, those who feel that stress of living is important have pointed out that various aspects of the complex circumstances of living are such that stresses may be quite different in one geographic area from another. Still other possible differences between persons residing in one area and another could be mentioned over and above any differences in diet that are known to exist. To some extent various of these criticisms can be countered and have been countered by investigators interested in epidemiologic investigation. For example, the issue of geography, climate and other environmental conditions as being perhaps of more importance than diet is in large measure contradicted by several sets of observations. First, Collumbine[53] has pointed out that the native Ceylonese in Ceylon show a low incidence rate of clinical coronary heart disease and subsist upon a low intake of dietary fat.

On the other hand, the Dutch burghers who reside in Ceylon have a much higher incidence of clinical coronary heart disease, an incidence not very different from that which characterizes their cohorts in Holland. If it were climatic or geographic conditions per se that were important in lowering the overall rate of coronary heart disease in Ceylon, there would be every reason to expect that the Dutch burghers would show to some extent, at least, the same protection that the Ceylonese are afforded. If the factors of climate and geography were paramount, the Dutch

burghers of Ceylon would be expected to show the same coronary disease attack rate as do the native Ceylonese. That they do not show the same rate is strong evidence that some factor other than geography, *climate, or other aspects of the environment* must be much more crucial in determining the coronary heart disease incidence rate. Similarly, evidence has been adduced by Bronte-Stewart and co-workers[54] that the coronary disease incidence rate in South Africa is much higher for the South African whites than it is for the Bantus in that area. Again, if geography, climatic conditions or similar environmental factors were paramount, it would be anticipated that the whites in South Africa would not fare so much more poorly than the Bantus with respect to the development of clinical coronary heart disease.

Analogous evidence bearing upon this same issue has been developed by others. For example, Larsen[55] has shown that Japanese residing in Western Countries experience a coronary disease incidence rate more nearly comparable with that of whites in such countries than they do with that of Japanese in Japan. If the ethnic factor were of paramount importance, one would anticipate that the Japanese who have migrated to the Western Countries should still show the protection that the ethnic factor *provides, which they apparently do not show* This type of evidence would counter another of the explanations alternative to diet which have been proposed for the difference in geographic incidence of coronary heart disease.

When all these considerations are weighed pro and con, we are still left with the conclusion that the epidemiologic incidence concerning the relationship of coronary heart disease with the diet is of itself not definitive That it produces valuable clues for direct experimental and clinical investigation is *not* denied even by those who are most vehemently opposed to acceptance of epidemiologic evidence that habitual diet is a factor in explaining the differences in coronary disease incidence rate in different countries. What is really of concern to the physician dealing with the problem of coronary heart disease in the United States is a knowledge of what role the dietary usually consumed by persons in the United States plays in the development of clin-

ical coronary heart disease. Further, his problem centers about what might be done by dietary means to alter the outlook for the development of coronary heart disease in individuals in this country by dietary alteration. Therefore, what is needed is evidence of a controlled character derived in typical individuals in the United States concerning the effect of dietary factors upon the evolution of clinical coronary heart disease and of the effect of alteration of such dietary factors under the practical circumstances which might be considered feasible in the usual pattern of living There are two major approaches that can be applied scientifically to this question Our interest truly lies in the evolution of serious clinical manifestations of coronary heart disease. Therefore the effect of diet can be studied directly with respect to the rate of development of clinical coronary heart disease. A comparison of diets in large sub-groups of the population could be made with subsequent followup of such sub-groups in the population for an adequate period of time to determine the incidence rate of coronary heart disease in relationship to the type and quantity of the various foodstuffs habitually consumed by the various sub-groups Such studies are by no means simple.

In a country like the United States there exists considerable heterogeneity in the population, heterogeneity in occupational distribution, heterogeneity with respect to climatic and other environmental conditions, and in other respects, all of which would make the question of matching the population sub-groups with respect to variables other than diet a task of major proportions Furthermore, the very task itself of performing a reasonable dietary survey is no small matter, leaving aside the matching upon other variables Up to the present time this type of study has not been accomplished. It is to be hoped that in time such a direct study will be done. One corollary of this type of study would be to alter the diet of a very large sub-segment of the population in a direction considered more favorable with respect to the outlook for coronary heart disease and then to compare the subjects who have altered their diet with a subgroup matched otherwise, but on an unaltered diet, with respect to the incidence rate of clinical coronary heart disease. In many ways such a study might be even more difficult than that of

burghers of Ceylon would be expected to show the same coronary disease attack rate as do the native Ceylonese. That they do not show the same rate is strong evidence that some factor other than geography, climate, or other aspects of the environment must be much more crucial in determining the coronary heart disease incidence rate. Similarly, evidence has been adduced by Bronte-Stewart and co-workers[54] that the coronary disease incidence rate in South Africa is much higher for the South African whites than it is for the Bantus in that area. Again, if geography, climatic conditions or similar environmental factors were paramount, it would be anticipated that the whites in South Africa would not fare so much more poorly than the Bantus with respect to the development of clinical coronary heart disease.

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When all these considerations are weighed pro and con, we are still left with the conclusion that the epidemiologic incidence concerning the relationship of coronary heart disease with the diet is of itself not definitive. That it produces valuable clues for direct experimental and clinical investigation is not denied even by those who are most vehemently opposed to acceptance of epidemiologic evidence that habitual diet is a factor in explaining the differences in coronary disease incidence rate in different countries What is really of concern to the physician dealing with the problem of coronary heart disease in the United States is a knowledge of what role the dietary usually consumed by persons in the United States plays in the development of clin-

each such study is formidable. The experiments involved are laborious, expensive, time-consuming and difficult to execute. Indeed, it is questionable that it is really possible to know the diet of a large series of patients under any circumstances other than institutionalization. Thus the type of rigorous proof desired may be outside the realm of practical reality. What, then, should be the position of the physician viewing the evidence concerning a favorable effect of a particular dietary alteration upon lipoprotein or Atherogenic Index values? Should he advise persons concerned with the prevention of clinical coronary heart disease (before or after an initial clinical manifestation) to make such a dietary alteration? There are three major possibilities which are of concern in appraising the prospect that a favorable dietary effect upon lipoprotein levels means a favorable effect upon coronary disease mortality. First, it is possible that lipoprotein level elevation and Atherogenic Index elevation may be direct causative factors in coronary heart disease, as much of the evidence suggests strongly that they are. If this be the true nature of the known association of coronary heart disease risk with Atherogenic Index value, then there would be every reason to expect that lowering of the Atherogenic Index value would lower the rate at which new sub-clinical coronary heart disease develops and hence lower the future risk of clinical coronary heart disease.

It is problematical at this time to know the extent to which such alteration in diet might be anticipated to reverse already existing coronary disease. Whether such disease can be reversed will need to be determined with direct experimental evidence. However, if the nature of the association is that which has just been considered, there is every reason to anticipate that lowering the levels of the lipoproteins will decrease the rate of development of *new* sub-clinical coronary heart disease. A second possibility is that some third factor, metabolic or otherwise, accounts for the elevation in lipoprotein-Atherogenic Index values and separately accounts for the development of coronary heart disease. It is conceivable that dietary alteration can affect the lipoprotein levels favorably but fail to affect this hypothetical third factor. In such an event the third factor, still being operative, might allow for the continued high rate of development of sub-

determining the effect of diet in matched population sub-groups without the question of *alteration* of diet.

While the results from such studies would be highly desirable, the many difficulties inherent in the direct approach to measurement of mortality from coronary heart disease in relation to diet or to alteration of diet are quite discouraging. As a result, experimental work upon the relationship of diet to coronary heart disease has taken quite another path, one that is highly favorable since not only does it provide information concerning the effect of diet upon known factors predisposing to coronary heart disease, but also it allows development of some insight into mechanisms by which these factors operate. Thus since the levels of lipoproteins from s_f0 to s_f400 are known to be directly related to the risk of future clinical coronary heart disease, it is entirely logical to determine the effect of any dietary factor or dietary alteration upon the level of all these lipoprotein classes. If increased intake of a particular dietary factor is found to be associated with elevation in level of any of these lipoprotein classes, then a decreased intake of this dietary element can, in general, be anticipated to reduce the level of the particular lipoprotein class and thereby to produce a favorable effect with respect to reduction of coronary heart disease risk. The reader will, of course, state that this represents a subtle transition from a demonstration of a favorable effect upon lipoprotein level to a favorable effect upon the risk of clinical coronary heart disease.

There can be no denial that the final and critical test of efficacy of any preventive or therapeutic measure is a direct test for reduction of *mortality* from coronary heart disease. This would require the study of a large series of cases, subdivided by careful randomization into two sub-groups. In one such sub-group a particular dietary alteration would need to be introduced whereas no such alteration would be made for the other sub-group. Comparison of coronary disease mortality rates at various follow-up intervals thereafter would then be made. This type of direct experiment constitutes the only final and rigorous proof. There is every reason to contemplate such studies of various dietary alterations to obtain the direct and final proof of efficacy. It must also be clear to the physician-reader that

the S_f20-400 and generally also the S_f12-20 lipoproteins. This latter group of patients is, on the average, characterized by a depression in the S_f0-12 lipoproteins. Before considering the specific dietary management of these two lipoprotein disorders, the general results of therapy must be emphasized. In every patient with these disorders where the lipoproteins have been lowered appreciably and maintained lowered (now 15 patients) two signal results have been achieved. First, new xanthomata have failed to develop although the patient had been developing new lesions up to the time the treatment was instituted. Second, old lesions not only did not increase in size but began to decrease in size Many of the old lesions disappeared entirely in a period of several months to two years. Lowering of lipoprotein levels in such patients was achieved in the main by dietary means. Thus, two different types of lipoprotein disorder, each characterized by a development of a lesion extremely similar to the atheroma, show regression of old lesions and inhibition of formation of new lesions when the lipoprotein levels are lowered. From the similarity of the atheroma to the lesions of xanthomatosis it would be a most reasonable and very likely expectation that atheromas would behave similarly when lipoprotein levels are lowered although perhaps at a different rate To be sure, the entire thesis of this book is being developed without the need to consider atheroma formation, since the relationships developed all hold at the clinical level without any dependence upon pathology Nevertheless, since it is probable that the mechanism by which lipoprotein levels and blood pressure come to be associated with clinical coronary heart disease is via their effect on atheroma formation, cognizance of the information concerning patients with xanthomatosis helps strengthen the view that lowering of elevated lipoprotein levels and elevated blood pressures offers great promise for retardation of development of coronary heart disease Other important indirect evidence has been presented in detail concerning the lowered coronary heart disease mortality in insured overweight persons who subsequently reduced in weight (see Chapter IX) In that same discussion it was demonstrated that the average lipoprotein and blood pressure elevations in overweight persons accounts for essentially all the excessive coro-

clinical coronary heart disease even though the dietary alteration had favorably affected the lipoprotein levels. No evidence whatever exists for any such third factor. It is simply being mentioned here as a hypothetical possibility, purely in the realm of speculation, since it would be unscientific to deny its possible existence.

It is strange that therapeutic nihilism in some quarters is so intense that the *possibility* of such a third factor is seized upon as a basis for denying any possible value of dietary reduction of blood lipoprotein levels in altering the rate of development of coronary heart disease. The position of such nihilists is completely unscientific and essentially hopeless to cope with on any rational basis A third possibility must be evaluated with respect to the alteration of lipoprotein levels by dietary means It is conceivable that dietary alteration may affect some hypothetical unproven other factor unfavorably with a net result of either no retardation of coronary heart disease development or even an acceleration of the process Such a possibility cannot be denied on scientific grounds, but the hypothetical noxious effect of diet on some hypothetical factor is at present a wholly undocumented speculative possibility. No facet of the overall picture of this disease suggests the existence of such a factor. Nihilism should not be allowed to retard clinical progress because of the remote possibility of existence of this factor. Were this type of nihilism allowed to operate broadly in medicine, the entire field of pharmaceutical therapeutics would long ago have ceased to exist.

Much indirect evidence argues strongly that reduction in intensity of the predisposing factors will reduce the rate of progression of coronary heart disease One source of such evidence is the study of patients with xanthoma tendinosum or xanthoma tuberosum Such patients exist in the population-at-large because of the fact that on a familial basis they have an enormous derangement of one or another classes of lipoproteins, the same lipoproteins which in the population-at-large are involved in the problem of coronary heart disease. The xanthoma tendinosum patients are characterized by massive elevations of the s_f0-12 lipoproteins and usually also the s_f12-20 lipoproteins, whereas the xanthoma tuberosum patients are characterized by elevation of

(1) The dietary fat intake, both with respect to quantity and type of fat consumed.

(2) The dietary carbohydrate intake.

(3) The dietary calorie intake.

Unfortunately, a great deal of the investigative work that has been done at the clinical level with dietary alteration has suffered from certain major failings. In some studies, multiple dietary variables were being studied at once, rendering interpretation of the results difficult or impossible. For example, patients advised concerning a restriction of the dietary fat intake have in many studies also been advised to restrict the total caloric intake, with the result that weight loss was occurring during the dietary experiment. Under such circumstances it is extremely difficult to draw any conclusions concerning the place of dietary fat restriction per se in management, since there existed the uncontrolled variable of marked weight loss. The inverse type of erroneous experiment has also been done. Thus in many studies where total caloric intake was restricted, there was a concomitant and essentially inadvertent restriction of fats, carbohydrates and protein. Effects upon lipoprotein levels observed during such caloric restriction may very well be the result of restriction of one or more of the specific components of the diet such as fat, protein, or carbohydrate. The practical implications of erroneous interpretation of such experiments can be enormous. If an effect truly attributable to fat restriction, for example, is credited to calorie restriction per se its applicability would be considered limited to those situations where calories could be restricted. In truth such applicability should have extended to numerous situations where calorie restriction is not feasible but where fat restriction is feasible. In many other dietary studies reported in the literature a variety of pharmacologically potent agents were prescribed at the same time the dietary modifications were made. Dietary data derived from such studies must necessarily be viewed with suspicion until and unless the possibility can be ruled out that the pharmaceutical agents being concurrently administered had no effect upon the biochemical variable under consideration.

Valid evidence concerning specific compositional factors in the diet is best derived from studies in which caloric intake is

nary heart disease in such persons. Furthermore conclusive evidence is available that correction of overweight has in general the effect of reducing elevated lipoprotein levels and elevated blood pressures. Thus it appears inescapable that the most probable basis for the beneficial effect of weight reduction is the lowering of lipoprotein levels and blood pressure. Certain general principles govern any approach to reduction of coronary heart disease risk by manipulation of lipoprotein levels and blood pressure. These principles apply not only to dietary methods but to any proposed pharmacologic approach or to their combination. The real objective of a dietary program would be to affect the combination of lipoprotein and blood pressure factors such that the *net risk* of clinical coronary heart disease will be lowered. Such net risk is the product of that due to the Atherogenic Index multiplied by that due to the blood pressure. Leaving the pressure consideration aside for the moment, coronary disease risk varies with Atherogenic Index. Therefore, should a particular dietary regimen lower the s_f*0-12* and s_f*12-20* lipoprotein levels but *raise* the s_f20-100 and s_f100-400 lipoprotein levels, the crucial issue would be whether or not the elevation in Atherogenic Index resulting from the rise in s_f20-400 lipoproteins was more than offset by the lowering in Atherogenic Index resulting from the fall in the s_f0-12 and s_f12-20 lipoproteins. This is simply a situation where one must consider whether the regimen does more good than harm If the focus is solely upon which lipoprotein classes fall in level, without consideration of possible rise in other classes, serious errors in medical management can and do result. This is by no means simply a hypothetical possibility Once it is assured that the dietary regimen has a *net* effect of lowering the Atherogenic Index, it is still necessary to insure that it does *not* raise blood pressure significantly, for if it does, the net effect upon coronary heart disease risk might still be unfavorable.

EFFECTS OF DIETARY FACTORS UPON SERUM LIPOPROTEIN LEVELS

Interest in dietary effects upon serum lipoproteins centers largely upon three factors:

content fall in level, e.g. s_f0-12, this may cause the total serum cholesterol level to fall even though a marked rise has occurred in lipoproteins poor in cholesterol content, e.g. s_f20-400. The opposite trend of s_f20-400 lipoproteins from that of s_f0-12 lipoproteins may be of sufficient magnitude to cause a marked rise in Atherogenic Index and hence coronary heart disease risk even though the blood cholesterol level has fallen. Therefore, the most satisfactory data come from those studies which provide information concerning the fate of each lipoprotein class of interest with respect to coronary heart disease under the influence of any particular dietary manipulation.

With respect to dietary fat intake, two separate questions of major interest exist today, with a large body of evidence now having built up concerning each. The first concerns the *quantity* of dietary fat consumed and the effect of this upon the several blood lipoproteins of importance for coronary heart disease. The second concerns the type of fat ingested rather than the quantity and the effect of type of fat upon the lipoprotein levels. Two features of dietary fats have been of especial interest; first, whether the fat is of animal or vegetable origin, and second, the degree of saturation of the fat. Since amount of fat and type of fat are the issues being considered, evidence must be reviewed for studies where all dietary alterations were made at isocaloric levels, so that weight loss is not involved. Where type of fat per se is the issue not only is it necessary that total calories remain constant but also that the total *quantity* of fat consumed daily remains constant. Further in such studies one is especially concerned about relatively long-term effects of diet. Therefore, dietary studies involving relatively few days on any particular regimen are hardly meaningful with respect to the longer term effects of interest, namely whether or not dietary alterations can be made which will produce and maintain lipoprotein alterations of a desirable character over a long period of time. Long term studies were performed during 1950 and 1951 which contrast diets high in fat intake with those low in total fat intake. Nichols and co-workers[40] have reported these carefully controlled studies. Diets high in fat of animal origin and those high in fat of vegetable origin have both been contrasted with low fat diets

maintained constant This is especially important since, for obscure reasons, many physicians and lay people alike equate dietary restriction with calorie restriction and are inclined to attribute nearly any effect obtained by dietary means to calorie restriction and weight loss. If dietary manipulation of coronary heart disease risk rested wholly upon calorie restriction and weight loss, *a great deal could be done clinically, but of greater* importance would be the need for management for the large fraction of the population in whom weight loss and calorie restriction is not feasible but in whom a high coronary heart disease risk still exists. Therefore, careful delineation of which dietary effects depend upon specific food factors and which, upon calorie restriction per se is of intense practical importance.

THE DIETARY FAT INTAKE

Dietary fat has been of interest with respect to coronary heart disease for a very long time, in part because of some of the apparent geographic associations between dietary fat intake, blood lipid levels, and coronary heart disease, early alluded to by Snapper[36] concerning such associations in China. However, many of the earlier studies of the relationship of diet with coronary heart disease via the association of both with blood lipid levels are now primarily of historical interest either (a) because the blood lipid methods utilized were very crude or (b) because the blood lipid measurements then available such as, for example, a serum cholesterol measurement, failed to provide adequate information concerning the fate of each of the important lipo-*protein classes with respect to dietary manipulation.* A blood lipid measurement which does not adequately reflect what is happening to all the lipoprotein classes between s_f0 and s_f400 can give rise to seriously erroneous impressions concerning the potential efficacy of the dietary alteration. Examples are now well known where a particular dietary manipulation can elevate the level of one band of lipoproteins while depressing the level of other bands. An approximate measure of the lipoprotein levels, such as the serum cholesterol level, reflects only part of the entire change. If certain lipoproteins rich in cholesterol

TABLE XXXVII

Long Term Effects of Diets High in Fat of Animal Origin Versus Diets Low in Total Fat Upon Serum Lipoprotein Levels and Atherogenic Index Values

(Both diets identical in calorie intake)*

Subject	During Diet High in Fat of Animal Origin	During Diet Low in Total Fat	Change
Mean S_f0-12 Lipoprotein Levels (mg/100ml)			
1	394	335	− 59
2	463	333	− 130
3	466	295	− 171
4	341	260	− 81
5	365	273	− 82
Mean for 5 Subjects	405.8	299.2	− 101.6
Mean S_f12-20 Lipoprotein Levels (mg/100ml)			
1	54	56	+ 2
2	100	62	− 33
3	105	63	− 42
4	32	30	− 2
5	65	44	− 21
Mean for 5 Subjects	71.2	51.0	− 20.2
Mean S_f20-100 Lipoprotein Levels (mg/100ml)			
1	126	169	+ 43
2	141	150	+ 9
3	129	132	+ 3
4	40	56	+ 16
5	137	142	+ 5
Mean for 5 Subjects	114.6	129.8	+ 15.2
Mean S_f100-400 Lipoprotein Levels (mg/100ml)			
1	125	308	+ 183
2	100	160	+ 60
3	72	102	+ 30
4	17	33	+ 16
5	56	73	+ 17
Mean for 5 Subjects	74.0	135.2	+ 61.2
Mean Atherogenic Index Values (in units)			
1	93	127	+ 31
2	106	98	− 8
3	100	81	− 19
4	50	47	− 3
5	82	73	− 9
Mean for 5 Subjects	86.1	85.2	− 0.9

* The low fat dietary period is a high-carbohydrate period, since carbohydrate calories replaced those lost from fat

in those studies. The study periods utilized by Nichols for each type of diet were sufficiently long that transitional effects resulting from dietary alteration were minimized. Five male subjects participated in that long-term dietary study, taking all meals at a hospital diet table, save for breakfast which was standard and was eaten at home. Samples of blood on all five subjects were drawn once weekly, divided into two aliquots, and analyzed in duplicate to minimize experimental errors. Furthermore, all dietary periods were of eleven or twelve weeks in duration. Therefore, the mean levels of lipoproteins for each particular dietary composition reflect no fewer than 22 blood analyses for each of the subjects studied. Since the overall dietary periods under consideration include the first week after the person was on the new diet, during which any transitional effects may have existed, the average effects measured for the entire period on a particular diet must actually have been even larger than reported, if the transitional periods are characterized by intermediary lipoprotein values. Therefore all the changes proved to be significant were evaluated in a conservative basis. The diets that were consumed by the individuals during these various periods do not represent formula diets. Instead they were diets prepared in a diet kitchen with kitchen-tested recipes and arranged in menus planned in such a manner that a person could enjoy meals over a long period of time with one or another of these diets What such diets may lack in ultimate chemical precision, they undoubtedly gain in provision of information concerning practical aspects of dieting over long periods under usual, physiologic circumstances of living. The data comparing the long-term lipoprotein levels on a diet high in fat primarily of animal origin and a diet low in fat are presented in Table XXVII. Maintenance of iso-caloricity was achieved by carbohydrate supplementation in the low fat period The regularity of fall in the level of s_f0-12 lipoproteins which occurs with substitution of a diet containing 103 grams of fat per day (93% of which is of animal origin) by a diet containing 18 grams of fat is notable. The s_f12-20 lipoproteins behave in general similarly to the s_f0-12 lipoproteins, falling in level when the high animal fat intake is replaced by a diet low in total fat intake The behavior of

TABLE XXXVIII

LONG TERM EFFECTS OF DIETS HIGH IN FAT OF ANIMAL ORIGIN VERSUS DIETS HIGH IN VEGETABLE OIL UPON SERUM LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES

(Both diets containing same total quantity of fat and calories)

Subject	*During Diet High in Fat of Animal Origin*	*During Diet High in Vegetable Oil*	*Change*
Mean S_f 12 Lipoprotein Levels (mg/100ml)			
1	394	290	− 104
2	463	316	− 147
3	466	284	− 182
4	341	269	− 72
5	365	299	− 66
Mean for 5 Subjects	405.8	291.6	− 114.2
Mean S_f 12-20 Lipoprotein Levels (mg/100ml)			
1	54	47	− 7
2	100	70	− 30
3	105	62	− 43
4	32	23	− 9
5	65	53	− 12
Mean for 5 Subjects	71.2	51.0	− 20.2
Mean S_f 20-100 Lipoprotein Levels (mg/100ml)			
1	126	142	+ 16
2	141	127	− 14
3	129	97	− 32
4	40	30	− 10
5	137	147	+ 10
Mean for 5 Subjects	114.6	108.6	− 6.0
Mean S_f 100-400 Lipoprotein Levels (mg/100ml)			
1	125	135	+ 10
2	100	109	+ 9
3	72	60	− 12
4	17	18	+ 1
5	56	61	+ 5
Mean for 5 Subjects	74.0	76.6	+ 2.6
Mean Atherogenic Index Value			
1	93	86	− 7
2	106	85	− 21
3	100	67	− 33
4	50	39	− 11
5	82	76	− 6
Mean for 5 Subjects	86.1	70.6	− 15.5

s_f20-100 and s_f100-400 lipoproteins accompanying this dietary shift was somewhat surprising. Both s_f20-100 and s_f100-400 lipoproteins rose appreciably, though variably among the subjects when the diet high in animal fat was replaced by that low in fat, but with the lost fat calories replaced by carbohydrate. The effect is sufficiently large to be well beyond any question of simply a sampling error, and it has been confirmed repeatedly, both here and elsewhere in the world[57, 58, 59]. There is no question that the low fat, high carbohydrate dietary period is associated with a rise in level of the s_f20-100 and s_f100-400 lipoprotein classes. Two possible explanations of the observed rise is s_f20-100 and s_f100-400 lipoproteins with this dietary shift are: (1) that a fat deficiency might be responsible, or (2) the possibility (which is now known to be correct) that the increase in carbohydrate intake necessary to maintain isocaloricity of the diet is itself responsible for the striking rise in s_f20-100 and s_f100-400 lipoproteins. The conclusion that it is the carbohydrate supplement rather than a possible fat deficiency which is responsible for the rise in s_f20-100 and 100-400 lipoproteins is based upon many sources of evidence to be developed below. First, however, it is important to compare two other dietary periods in this same study of Nichols and co-workers These two periods, again isocaloric, so that weight loss did not occur, both provided the same total quantity of dietary fat but the source and type of fat differed markedly in these two periods. Thus, approximately 100 grams of fat were present in the daily diet of both periods In one case the fat was primarily from animal sources, whereas the fat was primarily from vegetable sources in the other dietary period. In the period of high vegetable fat ingestion it was the liquid, relatively unsaturated cottonseed oil which was utilized The lipoprotein comparisons for these two dietary periods are presented in Table XXVIII It is to be noted from these data that the shift from 100 grams of fat primarily from animal sources to 100 grams of fat primarily in the form of vegetable oil, but with the total caloric intake and fat content of the diet maintained constant, that the s_f0-12 and s_f12-20 lipoprotein levels fell and did so to essentially the same extent as they did when the diet providing 100 grams of fat of animal origin was replaced by a low fat diet.

urated fatty acids in vegetable oil? Second, is the elevation in S_f20-100 and 100-400 lipoproteins observed on the high carbohydrate intake in contrast with the levels observed on both the diet high in animal fat and on that high in vegetable oil due to the increased carbohydrate intake per se or to some type of deficiency in the low fat, high carbohydrate diet?

With respect to the first question, there exists a very important corollary, namely, whether the addition of vegetable oil to a diet *unaltered in animal fat content* can be expected to overcome the noxious lipoprotein-elevating effect of a diet high in fat of animal origin. If vegetable oil provides some hypothetical positively beneficial substance, then it would be anticipated that S_f0-12 and S_f12-20 lipoprotein levels would *rise* when the vegetable oil diet is replaced by a low fat diet, since the hypothetical protective substance would be absent. The direct studies (see Tables XXVII and XXVIII) show that *no such rise* was observed upon shifting from the diet high in vegetable oil to that low in total fat intake. This militates strongly *against* the concept that any beneficial, protective substance exists in vegetable oil which helps to reduce S_f0-12 and S_f12-20 lipoprotein levels. On the other hand, if the animal fat contains a possible noxious substance, the S_f0-12 and S_f12-20 lipoprotein levels would be expected to fall comparably *either* with a replacement of the animal fat by vegetable oil or by a shift from a diet high in animal fat to a diet low in total fat intake. *This is precisely what is observed in carefully controlled studies.* It is reasonable to conclude, therefore, that fat of animal origin contains some factor (or factors) endowed with the noxious capability of elevating S_f0-12 and S_f12-20 lipoprotein levels. Several other investigators throughout the world have in recent years studied the differences between diets high in fat of animal origin and those high in oil of vegetable origin, utilizing the serum cholesterol level as a criterion of effects of various diets upon the blood lipoproteins. As a result of statements in the reports of some of these investigations there is current a notion in some quarters that certain vegetable oils contain a beneficial substance capable of lowering serum cholesterol levels. While the serum cholesterol level is not an adequate guide for blood lipoprotein response, the

Further, the s_f20-100 and s_f100-400 lipoprotein levels did not rise when vegetable oil was used to replace the animal fat instead of the use of carbohydrate for such replacement. Therefore, a diet which maintains the fat intake constant but which replaces animal fat with vegetable oil is completely like the low fat diet in *one respect,* namely that both diets are characterized by the same degree of lowering of the s_f0-12 and s_f12-20 lipoproteins when contrasted with a diet high in animal fat. The diet high in vegetable oil and the low fat diet (high in carbohydrate), however, *differ* in another very important respect, namely, whereas the s_f20-100 and s_f100-400 lipoprotein levels rise when carbohydrate is used as the replacement for the animal fat, they do not rise when vegetable oil is the replacement In summary, the s_f0-12 and s_f12-20 lipoproteins are at the same level on a diet high in vegetable oil or a diet high in carbohydrate, in both of which cases the levels are much lower than on the diet high in animal fat The s_f20-100 and s_f100-400 lipoproteins are at essentially the same level on a diet high in animal fat or vegetable oil, in both cases much lower than on a diet high in carbohydrate. All four classes of lipoproteins are of great importance because of their predictive association with clinical coronary heart disease. Hence, a dietary factor that affects the blood level of any one of them must be carefully weighed in any program designed to alter the risk of coronary heart disease. The remarkable dissociation between the effect of dietary factors on the s_f0-12 and 12-20 lipoproteins from the effect on the s_f20-100 and 100-400 lipoproteins points up the critical necessity of knowledge, for a particular dietary factor, of what it does to all of these lipoprotein classes. Reliance upon any crude measure which fails to discern opposite trends in level for one class of lipoproteins from those for other classes is of real clinical danger

Two fundamental questions of immediate clinical importance present themselves as a result of these findings with respect to diet. First, is the marked elevation in s_f0-12 and s_f12-20 lipoprotein levels on a diet high in animal fat relative either to one high in vegetable oil or to a low fat diet the result of action of some noxious factor in, or attribute of, animal fat or is it a manifestation of a deficiency of some factor such as the unsat-

a rise in the serum level of S_f20-100 and S_f100-400 lipoproteins on a high carbohydrate diet would elevate the blood cholesterol level, *provided* no fall in the level of other cholesterol-containing lipoproteins obscured this rise. When Ahrens shifted his patient isocalorically from a diet where 70% of the calories were from corn oil to one where only 10% of the calories came from corn oil, he was, in effect, shifting the patient from a very low carbohydrate diet to a very high carbohydrate diet. This increase in carbohydrate intake is itself quite adequate to account for the rise in blood cholesterol levels (via raising S_f20-100 and S_f100-400 lipoprotein levels) he observed without invoking the conclusion he drew that corn oil in large amounts is beneficial. His "positive" effect of corn oil is almost certainly the effect of lowering the carbohydrate intake of the patient.

Beveridge and co-workers[63] did short-term experiments of a somewhat similar nature to those of Ahrens. They showed that the blood cholesterol level fell when a low-fat diet was compared with a usual mixed diet Then when a large fraction of the carbohydrate of the low-fat diet was replaced by corn oil, they observed a further lowering of the serum cholesterol level. This lowering was attributed by Beveridge and co-workers to the beneficial effect of corn oil. No consideration was given by them to the possibility that the lowering of blood cholesterol levels might have been the result of the simultaneous removal of a large amount of the carbohydrate from the diet Since the removal of a great quantity of dietary carbohydrate in the Beveridge experiment would be expected to lower the S_f20-100 and S_f100-400 lipoprotein levels, and hence lower the blood cholesterol level because of the cholesterol content of these lipoproteins, there is no indication whatever for them to have attributed the observed changes to any presumed beneficial effect of corn oil Numerous other studies abound in the medical literature purporting to show a positively beneficial effect of some substance in vegetable oils, but essentially all of them suffer from the oversights described for the specific studies considered here.

At present there exists *no* valid evidence for the existence of a beneficial factor in vegetable oils or for an "essential" position of the vegetable oils in the human dietary with respect to the phe-

erroneous notions do not arise from this source, but rather from faulty interpretation of the experimental findings. Thus Kinsell[60] replaced animal fats with such vegetable oils as corn oil and observed a lowering of the serum cholesterol level. He drew the conclusion that there must be something positively beneficial about corn oil. Since corn oil contains an appreciable quantity of the unsaturated fatty acid, linoleic acid, he has advanced the idea that such unsaturated fatty acids as linoleic acid are "essential" fatty acids for the human with respect to the control of serum cholesterol levels. Kinsell apparently did not even consider seriously the alternative explanation of a noxious substance in fat of animal origin. Further, his studies were not controlled by the inclusion of a comparison of the high vegetable oil intake with a low-fat intake. Therefore there is no valid reason to consider from his work that linoleic acid is "essential" with respect to the maintenance of low serum cholesterol levels nor to consider that vegetable oils contain any positively beneficial agent capable of effecting a lowering of blood lipoprotein levels

Ahrens and his co-workers[61] studied patients on formula diets, with variation in the type of fat ingested and in the fraction of the total caloric intake provided by fat He reported for one patient that, when the proportion of total calories in the diet was varied upward from 40% to 70% and downward from 40% to 10%, while maintaining protein and total calorie intake constant, there was a rise in blood cholesterol level on the diet with 10% of the calories contributed by corn oil and a prompt decline in blood cholesterol level on the diet in which 70% of the calories were contributed by corn oil. He concluded "the reduction in lipid levels may be more pronounced with a high intake of certain specific fats." There is clearly implied in this statement that a fat such as corn oil provides some specific beneficial agent. There is no reason to accept this conclusion, from data such as those of Ahrens and co-workers. In the studies of Nichols and co-workers[18] (See Table XXXVII) it was found that a high carbohydrate intake is generally associated with a rise in the serum level of S_f20-100 and S_f100-400 lipoproteins These particular lipoproteins have cholesterol in them to the extent of approximately 13% by weight[62]. Therefore it would be anticipated that

for a decision as to whether dietary cholesterol itself might be the noxious agent involved in diets high in animal fat. Ahrens[85] has presented important evidence that *saturated* vegetable fats behave more like animal fats with respect to effect upon blood lipids when they do like the most unsaturated vegetable oils such as corn oil He suggested that perhaps the saturated fats may themselves be the noxious substances. It is certainly true that animal fats (*excluding* marine animal fats) are, on the average, more highly saturated than are such vegetable fats as unhydrogenated corn oil, cottonseed oil, and safflower oil. Bronte-Stewart and co-workers[86] found that *hydrogenated* groundnut oil produced higher blood cholesterol levels in human subjects than did dietary intake of equivalent amounts of unhydrogenated ground-nut oil However, they also found that the effect of hydrogenated ground-nut oil in raising blood cholesterol levels was slight compared with that produced by the dietary intake of the same *quantity* of fat in the form of egg-yolks.

It appears at present that the natural fats of animal origin such as dairy fat, meat fat, and egg fat have the greatest effect in elevation of s_f0-12 and s_f12-20 lipoprotein levels. Saturated vegetable fats, either those occurring naturally such as coconut oil or those produced by hydrogenation of unsaturated oils, have an adverse effect upon s_f0-12 and s_f12-20 lipoproteins but probably not to the same extent as the *animal* fats. The unsaturated vegetable oils, while *not beneficial* with respect to lowering of s_f0-12 and s_f12-20 lipoprotein levels, are at least neutral in this regard This latter fact is of itself of tremendous practical consequence, since it allows for the incorporation of vegetable oils into a diet (with attendant increase in palatability and satiety value) that is still adequately restricted in saturated vegetable fas and animal fats to achieve the desirable lowering of elevated s_f0-12 and s_f12-20 lipoprotein levels

DIETARY CARBOHYDRATE INTAKE

The second major problem involved in the effects of diet upon serum lipoprotein levels centers around the elevation of s_f20-100 and s_f100-400 lipoprotein levels during the low fat-

nomenon of control of blood lipid or lipoprotein levels It is clear from all studies that vegetable oils differ from animal fats, with all the evidence pointing to a noxious effect of the fats of animal origin rather than to a beneficial agent in the vegetable oil. The corollary question of whether or not the noxious effect of animal fat can possibly be overcome by *supplementation* of the diet by vegetable oil *without* removal of part or all of the animal fat from the diet comes up repeatedly. The experiments discussed up to this point do not of themselves allow for an answer to this highly pertinent question since they involved the *replacement* of animal fat by vegetable oil. Some poorly controlled studies have been reported in the literature where ostensibly a *supplement* of vegetable oil was provided in the daily diet and where a fall in blood lipid levels was observed. However, review of the protocols of such studies showed that these were actually *replacement* experiments, where either dietary animal fat or carbohydrate or both were *lowered* concurrently with the supposed "supplementation" of the diet by vegetable oil. Since no light is shed upon the problem at hand by such studies they do not merit specific comment here. One carefully performed supplementation study has recently reported by Perkins and Wright[64]. These workers provided a supplement of 50 grams of safflower oil in the diet of 24 subjects for a period of 6 to 7 weeks Safflower oil is very rich in linoleic acid, the fatty acid claimed by Kinsell to be "essential" for lowering of the blood cholesterol level. *No lowering of cholesterol levels could be demonstrated to occur as a result of safflower oil supplementation* in the careful study of Perkins and Wright. It therefore appears necessary to conclude that the noxious effect of animal fat cannot be overcome by provision of a vegetable oil supplement, even when that vegetable oil is one of the richest in its content of linoleic acid.

It is a matter of practical, as well as academic, interest to identify the nature of the noxious agent (or agents) present in fat of animal origin which can effect an elevation of S_f0-12 and S_f12-20 lipoprotein levels In most of the reported studies with dietary animal fat, the diet also provided a reasonably high content of cholesterol *per se*. None of the studies discussed allow

for a decision as to whether dietary cholesterol itself might be the noxious agent involved in diets high in animal fat. Ahrens[65] has presented important evidence that *saturated* vegetable fats behave more like animal fats with respect to effect upon blood lipids when they do like the most unsaturated vegetable oils such as corn oil He suggested that perhaps the saturated fats may themselves be the noxious substances. It is certainly true that animal fats (*excluding* marine animal fats) are, on the average, more highly saturated than are such vegetable fats as *unhydrogenated* corn oil, cottonseed oil, and safflower oil. Bronte-Stewart and co-workers[66] found that *hydrogenated* groundnut oil produced higher blood cholesterol levels in human subjects than did dietary intake of equivalent amounts of *unhydrogenated* ground-nut oil However, they also found that the effect of hydrogenated ground-nut oil in raising blood cholesterol levels was slight compared with that produced by the dietary intake of the same *quantity* of fat in the form of egg-yolks.

It appears at present that the natural fats of animal origin such as dairy fat, meat fat, and egg fat have the greatest effect in elevation of s_f0-12 and s_f12-20 lipoprotein levels. Saturated vegetable fats, either those occurring naturally such as coconut oil or those produced by hydrogenation of unsaturated oils, have an adverse effect upon s_f0-12 and s_f12-20 lipoproteins but probably not to the same extent as the animal fats The unsaturated vegetable oils, while *not beneficial* with respect to lowering of s_f0-12 and s_f12-20 lipoprotein levels, are at least neutral in this regard This latter fact is of itself of tremendous practical consequence, since it allows for the incorporation of vegetable oils into a diet (with attendant increase in palatability and satiety value) that is still adequately restricted *in* saturated vegetable fas and animal fats to achieve the desirable lowering of elevated s_f0-12 and s_f12-20 lipoprotein levels

DIETARY CARBOHYDRATE INTAKE

The second major problem involved in the effects of diet upon serum lipoprotein levels centers around the elevation of s_f20-100 and s_f100-400 lipoprotein levels during the low fat-

high carbohydrate dietary periods. Is this elevation the result of the high carbohydrate intake or the result of some type of deficiency encountered because of the low fat intake? Data were already present for weight reduction studies (see Chapter IX) which help provide the answer to this question. In those studies a 1000 calorie, low fat, low carbohydrate diet was utilized. If fat deficiency were responsible for an elevation in s_f20-100 and s_f100-400 lipoproteins, it would have been anticipated that the s_f20-100 and s_f100-400 would have become elevated in level during the weight reduction program, *but this did not occur.* Instead the s_f20-100 and s_f100-400 lipoprotein levels *fell* during the weight reduction period. Since the 1000 calorie diet is a low-carbohydrate diet, this is precisely the result that would have been anticipated if these lipoprotein classes are sensitive to the dietary carbohydrate intake, rising with increased carbohydrate intake and falling with decreased carbohydrate intake. The clinical experience of the author, in numerous patients, has consistently confirmed this conclusion, namely that s_f20-100 and s_f100-400 lipoprotein levels are largely controlled by the dietary carbohydrate intake. Indeed the most effective dietary procedure for reducing elevated s_f20-100 and s_f100-400 lipoprotein levels is the reduction in the patient's habitual dietary carbohydrate intake.

The mechanism by which carbohydrate excess in the diet produces elevation of s_f20-100 and s_f100-400 lipoprotein levels remains unexplained at this time. Two possible explanations currently under consideration are that (a) dietary carbohydrate in abundance spares the utilization of fat from s_f20-100 and s_f100-400 lipoproteins from the blood for energy purposes and hence results in an increase in their levels or (b) that the conversion of dietary carbohydrate to fat either for storage or utilization involves a transport phase during which the s_f20-100 and s_f100-400 lipoprotein levels are elevated. Whatever be the precise biochemical mechanism, the practical implications of the carbohydrate effect for the prevention and treatment of clinical coronary heart disease are extensive.

THE CALORIE INTAKE

Thus far consideration has been given to the dietary intake of fat, both with respect to quantity and origin, and the dietary intake of carbohydrate. All of the studies which show the effects of alteration of these dietary factors have been done at isocaloric levels, with the subjects neither gaining nor losing weight. Hence, calories were not involved as a variable. It cannot be overemphasized that, *without* alteration of weight or calorie intake, blood lipoproteins *can* be altered by certain dietary shifts. However, the lipoprotein alterations which occur when calorie intake and weight are altered are of much interest. The changes in blood lipoproteins both in experimental alteration of weight and in the "natural" experiment where individuals gain or lose weight over a long period of time are presented in Chapter IX in the general discussion of overweight, correction of overweight, and their relationship to lipoprotein levels. Associated with a correction of overweight by calorie restriction there occurs a fall in blood level in all the major classes of lipoproteins, s_f-12, 12-20, 20-100 and 100-400. In the light of the immediately previous discussion, the probable explanation for the fall in lipoproteins which is observed when an individual who is overweight goes on a calorie restricted diet can be evaluated. A person who is habitually eating more calories than he needs to maintain an ideal weight is taking in too many calories either in the form of protein, of fat, or of carbohydrate or of some combination of these. Of these three, it is most likely that any real excess in calories is coming in the form of an excess of fat and/or carbohydrate as a result of the types of habitual diets generally consumed by Americans. Of the excess fat which would be consumed, undoubtedly a fair share would be of the relatively saturated varieties, either animal fat or hydrogenated vegetable fat. This being the case such a person might be anticipated to show, in general, some elevation in the s_f0-12 and 12-20 levels as a result of his habitual excessive fat intake, or some elevation in the s_f20-100 and 100-400 levels as a result of a habitual excess carbohydrate intake, or both. Therefore, when such a person goes on a calorically restricted diet in the effort to correct over-

high carbohydrate dietary periods. Is this elevation the result of the high carbohydrate intake or the result of some type of deficiency encountered because of the low fat intake? Data were already present for weight reduction studies (see Chapter IX) which help provide the answer to this question. In those studies a 1000 calorie, low fat, low carbohydrate diet was utilized. If fat deficiency were responsible for an elevation in s_f20-100 and s_f100-400 lipoproteins, it would have been anticipated that the s_f20-100 and s_f100-400 would have become elevated in level during the weight reduction program, *but this did not occur. Instead the s_f20-100 and s_f100-400 lipoprotein levels fell during* the weight reduction period. Since the 1000 calorie diet is a low-carbohydrate diet, this is precisely the result that would have been anticipated if these lipoprotein classes are sensitive to the dietary carbohydrate intake, rising with increased carbohydrate intake and falling with decreased carbohydrate intake. The clinical experience of the author, in numerous patients, has consistently confirmed this conclusion, namely that s_f20-100 and s_f100-400 lipoprotein levels are largely controlled by the dietary carbohydrate intake. Indeed the most effective dietary procedure for reducing elevated s_f20-100 and s_f100-400 lipoprotein levels is the reduction in the patient's habitual dietary carbohydrate intake.

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saturated vegetable fat can be replaced by any of a variety of vegetable oils such as cottonseed oil, corn oil, safflower oil, sunflower oil, soya oil, or peanut oil, without fear of producing a rise in lipoproteins through addition of these vegetable oils. In other words, the vegetable oils of these type are essentially without any effect, favorable or unfavorable. However the absence of any adverse or beneficial effect is in itself a highly beneficial feature, since this means that the diet that is possible for such an individual produces no real loss in palatability, satiety value, and enjoyment relative to that which utilizes the animal fats. Such a diet is much more readily accepted and enjoyed by a patient than would be a low fat diet. If the patient with elevated s_f0-12, or s_f0-20 lipoprotein levels is not overweight, he can ill afford to lose any of his dietary calories by simple removal of the animal or saturated fat from his diet. He needs replacement of calories to avoid weight loss. But loss of weight has been shown above *not* to be an essential part of this problem of lowering the s_f0-12 or s_f0-20 lipoproteins. It is rather a question of the type of dietary fat consumed Therefore, even though such an individual maintains his calories by replacement with one of the vegetable oils and thereby maintains his weight, he will generally experience a favorable reduction in lipoprotein levels. On the *other hand*, if such a patient is overweight, there would be every reason to attempt to reduce some of the calories in his diet and in this attempt to concentrate upon those calories deriving from saturated vegetable fat or animal fat, since they are for him the offenders involved in maintaining high s_f0-12 and 12-20 levels.

There exist many persons who are characterized by low levels of the s_f0-12 and 12-20 lipoproteins, but who demonstrate very high levels of s_f20-100 of s_f100-400 lipoproteins or both The elevation in these classes of lipoproteins is sufficient in many such patients to produce markedly elevated Atherogenic Index values and, hence, high coronary heart disease risks in spite of their low levels of the s_f0-12 and 12-20 lipoproteins In this type of patient efforts to decrease the coronary heart disease risk through the advocacy of a low fat diet or of a replacement of animal fat with vegetable oil will be to no avail in the vast majority of cases, for the lipoproteins that are elevated in these persons are not

weight and when he reduces some of the animal fat (or saturated fat intake) in his diet as well as some of the carbohydrate intake in his diet, it is not surprising that we should see an average trend downward of the four classes of lipoproteins. During calorie restriction dietary alterations are being made which are *known* to affect either one group of lipoproteins or another, or both. Whether or not any factor beyond the reduced animal fat intake or the reduced carbohydrate intake or both is responsible for the fall in lipoproteins which occurs when an individual restricts dietary calories and loses weight cannot be stated. However, there exists no positive evidence that any such effect operates over and above that which can be explained by the animal fat restriction and/or the carbohydrate restriction in such a low calorie diet. The overweight individual who is taking in too much animal, or saturated, fat and too much carbohydrate habitually has of course the best opportunity to reduce lipoprotein levels since he can to good advantage lower two types of substances in the diet which are known to have unfavorable influences upon the blood lipoproteins, the Atherogenic Index, and the coronary heart disease risk.

THE PRACTICAL CLINICAL APPLICATIONS OF THE DIETARY FINDINGS

It is evident that no single dietary regimen can be prescribed that will cover all the types of situations encountered with respect to blood lipoprotein distribution in the effort to reduce clinical coronary heart disease risk. Thus there are individuals who carry an excessive risk of coronary heart disease almost wholly because of a marked elevation of the s_f*0-12* and *12-20* lipoproteins, and who show either usual or lower-than-usual levels of the s_f*20-100* and *100-400* lipoproteins. For this type of individual there is excellent reason to prescribe a trial of a diet restricted in fat of animal origin or saturated fat of vegetable sources. In many such individuals the lipoproteins of the s_f0-20 class will fall markedly, there will be a corresponding improvement in the Atherogenic Index, and the patient may be expected to benefit. The calories lost from the animal fat or

saturated vegetable fat can be replaced by any of a variety of vegetable oils such as cottonseed oil, corn oil, safflower oil, sunflower oil, soya oil, or peanut oil, without fear of producing a rise in lipoproteins through addition of these vegetable oils. In other words, the vegetable oils of these type are essentially without any effect, favorable or unfavorable. However the absence of any adverse or beneficial effect is in itself a highly beneficial feature, since this means that the diet that is possible for such an individual produces no real loss in palatability, satiety value, and enjoyment relative to that which utilizes the animal fats. Such a diet is much more readily accepted and enjoyed by a patient than would be a low fat diet. If the patient with elevated s_f0-12, or s_f0-20 lipoprotein levels is not overweight, he can ill afford to lose any of his dietary calories by simple removal of the animal or saturated fat from his diet. He needs replacement of calories to avoid weight loss But loss of weight has been shown above not to be an essential part of this problem of lowering the s_f0-12 or s_f0-20 lipoproteins. It is rather a question of the type of dietary fat consumed Therefore, even though such an individual maintains his calories by replacement with one of the vegetable oils and thereby maintains his weight, he will generally experience a favorable reduction in lipoprotein levels. On the other hand, if such a patient is overweight, there would be every reason to attempt to reduce some of the calories in his diet and in this attempt to concentrate upon those calories deriving from saturated vegetable fat or animal fat, since they are for him the offenders involved in maintaining high s_f0-12 and 12-20 levels.

There exist many persons who are characterized by low levels of the s_f0-12 and *12-20 lipoproteins*, but who demonstrate very high levels of s_f20-100 *of* s_f100-400 lipoproteins or both. The elevation in these classes of lipoproteins is sufficient in many such patients to produce markedly elevated Atherogenic Index values and, hence, high coronary heart disease risks in spite of their low levels of the s_f0-12 and 12-20 lipoproteins. In this type of patient efforts to decrease the coronary heart disease risk through the advocacy of a low fat *diet or* of a replacement of animal fat with vegetable oil will be to no avail in the vast majority of cases, for the lipoproteins that are elevated in these persons are not

sensitive to the composition or quantity of fat in the diet. Rather, they are very sensitive to the quantity of carbohydrate in the diet. Therefore, in clinical practice, such patients should be treated with a diet restricted in carbohydrate. Here again, vegetable oils represent a very useful agent in the diet, for the calories that are lost from carbohydrate can be supplanted by those from vegetable oils with excellent palatability of the diet. This is expecially important in the patient who is already at ideal weight or is *underweight and cannot afford to lose such calories* For the patient with high s_f20-100 and 100-400 lipoprotein levels who is overweight and who can and should lose some of the calories, his caloric restriction and the correction of his overweight can be made more *meaningful* if such caloric restriction is focussed on the carbohydrate intake.

Lastly, physicians will encounter patients who have what may be called "across the board" elevations of all four important classes of lipoproteins These patients require a still different dietary approach. If the patient is overweight some of the calories which are in excess should be deleted from the diet both in the form of animal fat and of carbohydrate. In this situation the calories lost require no replacement. If such a patient is not overweight, then the appropriate diet still would require reduction of the intake of animal fat (or saturated vegetable fats) on *the one hand, and* of *carbohydrate on the other.* This means that supplementation of the calories required to maintain weight would have to come from vegetable oils. If attention is paid only to one class of lipoproteins, full advantage of the dietary approach is hardly being taken for the particular patient, and in certain instances serious errors of management can eventuate. For example, if a patient has an elevation of s_f20-100 and 100-400 lipoproteins (the carbohydrate-sensitive group), and if the physician, failing to realize the indication for a low-carbohydrate diet, prescribes a low fat diet for this patient, he will fail to accomplish his objective because he is not changing any dietary factor that can be expected to influence those lipoproteins of importance in such a patient. Secondly, he may do some real harm because of the fact that many patients who restrict fat in their diets replace the fat freely with carbohydrate. In this particular

type of patient, sensitive to carbohydrate, the additional carbohydrate can be regarded as an insult which will raise s_f20-100 and s_f100-400 lipoprotein levels still further. There are many patients, however, who can replace *some* of their animal fat with carbohydrate in the effort to lower their s_f0-20 lipoproteins by animal fat (or saturated fat) restriction because they are not very sensitive to the carbohydrate effect and will not experience any appreciable rise in s_f20-100 and 100-400 lipoproteins. This can only be determined by direct trial in each particular patient. However, it is through the careful assessment both of the s_f0-20 and the s_f20-400 lipoproteins that one can, with certainty rather than with guesswork, determine whether a particular dietary regimen is influencing a patient in a favorable direction. The lipoprotein measurements can aid the physician to appreciate whether further dietary changes are still indicated, including the type of dietary changes indicated to try to achieve desired results.

The irrational, blanket use of a particular dietary regimen in all persons irrespective of lipoprotein distribution is *not to be* condoned Such generalizations as "we all eat too much fat," or "we all eat too much animal fat" merely reflect a lack of understanding of major progress in the understanding of dietary factors in relation to risk of coronary heart disease. *There is of* course some element of truth in such generalizations, but there is also a considerable element of falsehood in them. For a large segment of the population the statement that "we eat too much carbohydrate" is much closer to reality Action based upon uncritical generalizations may do almost as *much medical* harm as good, and in individual cases we can be certain that more harm than good will result It can be regarded as fortunate that enough knowledge is now available for a critical approach to dietary management and such knowledge should be fully utilized by the practising physician

Chapter XI

CIGARETTE SMOKING AND CORONARY HEART DISEASE

It is commonplace in medical practise to find that physicians advise patients with clinically-manifest coronary heart disease to cut down on smoking, especially those individuals with a history of heavy cigarette smoking. Evidently, the impression has been widespread medically that in some way cigarette smoking is unfavorable for the patient with clinically documented coronary heart disease. Some of this advice is based upon the suspicion that tobacco may produce coronary artery vasoconstriction, which, in the face of an already embarrassed coronary blood flow, is regarded as highly unfavorable. All this pertains to the person with already-established clinical coronary heart disease. Of even greater importance is the question of whether or not cigarette smoking is associated with any increased risk of *future* clinical coronary heart disease in the vast bulk of the population-at-large in overt health. This question might be put another way, "Does cigarette smoking accelerate the rate of development of *subclinical* coronary heart disease?" On this question general medical opinion has for long been divided, largely, of course, because sound evidence upon which a meaningful answer could be based simply was unavailable. Several significant avenues of approach may be contemplated in the effort to answer this question. Information is now available from scientific observation not only to answer the question in the affirmative, namely that cigarette smoking is associated with acceleration of the rate of development of subclinical coronary heart disease, but also to understand the probable mechanisms through which the effect is mediated.

RETROSPECTIVE EVIDENCE CONCERNING CIGARETTE SMOKING

The study of smoking histories in persons who have survived a clinical manifestation of coronary heart disease and in persons otherwise matched (by age, sex, etc.), but without clinical coronary heart disease has been performed by Gertler and White[36] and by Yater and co-workers[22]. The Gertler and White study was done on their series of 97 men who had had a myocardial infarction below the age of 40 years and who had survived the episode. A matched control group of men was also questioned by these workers with reference to smoking habits. While it was found that both the myocardial infarction survivors and the men of the matched control group had appreciable numbers of cigarette smokers amongst them, two facts became evident as a result of the questioning concerning cigarette-smoking habits:

(1) The average number of cigarettes habitually smoked by the group of myocardial infarction survivors was approximately 50% higher than the average number of cigarettes habitually smoked per day by the matched control group.

(2) There were approximately twice as many non-smokers among the matched control men as there were in the group of survivors of myocardial infarction.

Yater and co-workers did a similar retrospective study in a series of men between 18 and 39 years of age who experienced a non-fatal [illegible]

Th[illegible]

gro[illegible] a matched control Army group of men. They found that amongst the myocardial infarction group 53% reported having smoked five or more cigarettes per day and for the matched control group 57% reported having smoked five or more cigarettes per day. However, a very striking difference was found when the groups were considered on the basis of having smoked ten or more cigarettes per day. There were 68% of the myocardial infarction group who reported smoking this much, whereas only 19% of the matched control group who reported smoking ten or more cigarettes per day.

The studies of Gertler and White and of Yater and co-workers are quite consistent with each other, both indicating

that heavy cigarette smoking was distinctly more frequent among the myocardial infarction cases than among their matched controls. Within the limitations of this type of study involving retrospective questioning, there appears, from the evidence, to exist an association between heavy cigarette smoking and subsequent coronary heart disease. There are, however, good reasons why such evidence by itself can be regarded as inadequate to establish the relationship between cigarette smoking and coronary heart disease. First, there is the possibility that the answers given by the myocardial infarction patients may, in part, have been influenced by their own suspicion that cigarette smoking had in some way contributed to their development of coronary heart disease. Under such circumstances there would have existed a tendency for this group to overestimate the average number of cigarettes smoked. Furthermore, since such evidence arises primarily from the study of *survivors* of myocardial infarction, there are missing from the series those persons who had not survived their myocardial infarction and who therefore were unable to provide answers concerning their smoking habits. The possible influence of this deletion is difficult to assess

Thus, the retrospective evidence, while highly suggestive of an association between cigarette smoking and later clinical coronary heart disease, is inconclusive A far more satisfactory approach is found in the *prospective* type of study, where a determination is made of the smoking habits of a large number of persons, preferably tens or hundreds of thousands, at a time when they are overtly in health and free of evidence of clinical coronary heart disease. Out of such a large series of persons in overt health there will, with the passage of time, grow a number of cases of *de novo* clinical coronary heart disease, some surviving, others not For *these* cases of clinical coronary heart disease the smoking history will have been known *in advance* of the clinical occurrence of coronary heart disease. Such smoking histories can neither be influenced by survivorship from the clinical episode nor by any preconceived notions of the subjects with respect to the possible relationship of cigarette smoking with coronary heart disease. In such a study the time required for a definitive answer is largely dependent upon the number of per-

sons in the original large group under observation. The larger the number of persons in overt health who are questioned concerning smoking habits, the sooner will there be a sufficient number of episodes of clinical coronary heart disease so that an analysis can be made of possible relationships between cigarette smoking and the risk of clinical coronary heart disease. Fortunately such a study has now been done on a very large scale by Hammond and Horn[67] of the American Cancer Society, with highly conclusive results.

In the American Cancer Society study field workers interviewed over 200,000 persons with respect to their smoking habits, that is, whether they had ever smoked, if yes, how much did they smoke and what (cigarettes, cigars, or pipes), and whether or not they quit smoking These findings were maintained on file and during the ensuing months and years a number of clinical episodes of coronary heart disease occurred in this very large population sample under study. The early findings from this study were published by Hammond and Horn in 1954[67]. The results showed clearly that men in their fifties and sixties who were regular smokers of cigarettes developed approximately 1½ to 2 times as many myocardial infarctions per thousand men per year as did those men who had never smoked cigarettes. Such evidence, derived by the questioning of a large sample of the population *first* and then observing *thereafter* who develops clinical coronary heart disease is free of all the criticisms that may be levelled at studies involving the questioning of men who have survived one or more episodes of clinical coronary heart disease. The Cancer Society evidence hardly leaves room for doubt or question concerning the existence of a positive association between *heavy cigarette* smoking and an excessive incidence rate of clinical manifestations of coronary heart disease. Yet consistently in certain quarters there has existed an intensive effort to belittle the significance of the highly important findings of Hammond and Horn.

One common statement concerning these studies is that the proof of a higher *incidence* rate of *clinical coronary* heart disease in regular cigarette smokers *than in* non-smokers does not *of itself* prove that cigarette smoking is a *cause* of clinical coronary

that heavy cigarette smoking was distinctly more frequent among the myocardial infarction cases than among their matched controls. Within the limitations of this type of study involving *retrospective* questioning, there appears, from the evidence, to exist an association between heavy cigarette smoking and subsequent coronary heart disease. There are, however, good reasons why such evidence by itself can be regarded as inadequate to establish the relationship between cigarette smoking and coronary heart disease. First, there is the possibility that the answers given by the myocardial infarction patients may, in part, have been influenced by their own suspicion that cigarette smoking *had in some way contributed to their development of coronary* heart disease. Under such circumstances there would have existed a tendency for this group to overestimate the average number of cigarettes smoked. Furthermore, since such evidence arises primarily from the study of *survivors* of myocardial infarction, there are missing from the series those persons who had not survived their myocardial infarction and who therefore were unable to provide answers concerning their smoking habits The possible influence of this deletion is difficult to assess

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THE BASIS FOR THE OBSERVED ASSOCIATION OF CIGARETTE SMOKING AND CORONARY HEART DISEASE

With the solidly-established finding that cigarette smoking *is* positively associated with excessive coronary heart disease, the prime question arises as to whether new, or independent, information is provided. Either cigarette smoking becomes associated with excessive coronary heart disease via a relationship of cigarette smoking with one of the already established factors in coronary disease development, or via some wholly new mechanism. The only factors that still stand critical testing for provision of *independent* information about the risk of an individual's developing clinical coronary heart disease are:

(1) The blood level of the S_f0-12, 12-20, 20-100, and 100-400 lipoproteins.

(2) The diastolic blood pressure.

It is therefore necessary to know whether cigarette smoking is or is not related to the level of any of these blood lipoproteins and whether or not it is related to the level of the diastolic blood presure If *no* such relationships exist, then it would follow that cigarette smoking must be *independently* related to the development of clinical coronary heart disease and that the smoking history of an individual provides *additional* information concerning his risk of future clinical coronary heart disease. If, on the other hand, demonstrable relationships exist between cigarette smoking and the blood lipoprotein levels, or between cigarette smoking and the diastolic blood pressure, or both, it becomes necessary to determine whether such relationships account for part or all of the observed relationship between cigarette smoking and the incidence rate of clinical coronary heart disease

CIGARETTE SMOKING AND BLOOD LIPOPROTEIN LEVELS

Direct experimental data are now available for a large scale study of humans which provide the extent of relationship of cigarette smoking with lipoprotein levels and atherogenic index values The results were originally reported on 461 persons[69],

heart disease. The reasoning behind such criticism is that possibly a certain type of individual is prone to develop clinical coronary heart disease and is (for reasons not given by the critics) the type of person who is likely to become a regular smoker of cigarettes. If this be true, it is argued, the proneness to coronary heart disease might still exist even if such a person either *had never taken up smoking or had quit smoking cigarettes.* No sound, scientific thinker would deny the validity of this *possible* explanation of the observed findings. Indeed such a possibility must always be considered in problems such as this one. But it would be the height of folly to forget the *other* possibility, which is *at least* equally likely, that cigarette smoking *is* one of the direct causes of an increased incidence rate of clinical coronary heart disease. In scientific medical problems such as this one the demonstration of a positive association between two variables, e.g. cigarette smoking and coronary heart disease *incidence rate, is an excellent first step. Whether the first item* (cigarette smoking) causes the second item (clinical coronary heart disease) or whether both items are separately caused by some third factor (cigarette smoking and coronary heart disease both being separate results of the metabolic makeup or personality makeup of the individual) can best be considered through appropriate further studies What is of prime importance is the realization that the clear-cut demonstration of a marked association between heavy cigarette smoking and subsequent clinical coronary heart disease is a monumental step forward in the elucidation of factors important in the development of coronary heart disease. Even if it should develop that cigarette smoking is *not* an actual cause of coronary heart disease, the information developed could not help but to lead to identification of *some* factor about smokers of cigarettes that leads them to show an inordinate average susceptibility to clinical coronary heart disease. Valuable leads such as this one are not so easily found as to allow for casual or summary dismissal of their importance.

TABLE XXXIX

LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES IN SMOKERS AND NON SMOKERS*

MEN (Category and Number of Men)	Mean S_f0-12 mg/100ml	Mean S_f12-20 mg/100ml	Mean S_f20-100 mg/100ml	Mean S_f100-400 mg/100ml	Mean Atherogenic Index (units)	Average Number of Cigarettes Per Day
486 men who never smoked	330.8	18.6	81.7	49.5	66.9	0
99 men who smoke fewer than 10 cigarettes per day	316.7	48.2	86.0	45.5	67.0	3.7
315 men who smoke 10-19 cigarettes per day	352.2	47.1	91.7	50.2	69.6	12.7
673 men who smoke more than 20 cigarettes per day	361.5	50.2	93.1	49.3	71.1	22.6
217 men who had given up cigarette smoking	326.7	17.3	87.8	52.8	66.8	0
126 men who smoked pipes or cigars or both, but no cigarettes	335.7	48.0	90.6	59.6	68.4	0
WOMEN (Category and Number of Women)						
128 women who never smoked	303.0	32.7	51.7	14.6	48.5	0
39 women who smoke fewer than 10 cigarettes per day	299.9	30.7	39.7	14.1	47.3	4.5
66 women who smoke between 10 and 19 cigarettes per day	318.8	36.1	51.1	12.1	49.6	12.1
45 women who smoke more than 20 cigarettes per day	325.0	39.4	47.7	10.3	49.3	21.0
13 women who had given up cigarette smoking	275.7	29.8	46.6	13.0	53.9	0

*Since the mean age of the various groups of men ranged from 32.6 to 36.5 years, all values were adjusted to 35.0 years. Similarly, for women all values were adjusted to 30.0 years

with extension and confirmation of the findings now in 2201 persons. These individuals were asked to fill out a questionnaire concerning their past and present smoking habits at the time they were undergoing a routine periodic medical examination at their place of employment. These persons had no idea of the purposes to which the questionnaire might be put nor were they aware of other measurements being made for correlation studies with the smoking history. It seems virtually certain that studies of the relationship of smoking habits with serum lipoprotein levels, conducted in this manner, could not conceivably been systematically biassed in one direction or another. In another part of this medical examination blood pressures were measured in a routine fashion and a sample of blood was withdrawn for lipoprotein and other biochemical analyses. The smoking history questionnaire provided data adequate to subdivide the entire population sample into those who never had smoked, those who smoked cigarettes (divided into sub-categories dependent upon the average number of cigarettes smoked per day), those who had been smokers of cigarettes but who had quit smoking, and those who smoked cigars and/or pipes, but not cigarettes. The lipoprotein and atherogenic index findings for the various categories of smokers and for non-smokers are presented in Table XXXIX Cigarette smokers among the men show highly significant elevations of s_f0-12 and s_f20-100 lipoproteins and of the atherogenic index in comparison with those men who never had smoked Further the group smoking cigarettes heavily (20 or more per day) showed higher values of these variables than did those who smoked fewer than 20 cigarettes per day. These data establish conclusively that cigarette smoking is positively associated with elevation in Atherogenic Index values and hence, that at least part of the association of cigarette smoking with a high incidence rate of coronary heart disease would be expected as a result of the cigarette smoking-atherogenic index relationship. Quantitative assessment of how large this part is will be made below

It is, of course, not unexpected that there will be those who can say that these data do not *prove* that cigarette smoking *causes* the observed elevation in s_f0-12 and s_f20-100 lipoproteins

TABLE XXXIX

LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES IN SMOKERS AND NON SMOKERS*

MEN (Category and Number of Men)	Mean S_f0 12 mg/100ml	Mean S_f12 20 mg/100ml	Mean S_f20-100 mg/100ml	Mean S_f100 400 mg/100ml	Mean Atherogenic Index (units)	Average Number of Cigarettes Per Day
486 men who never smoked	336.8	48.6	81.7	49.5	66.9	0
99 men who smoke fewer than 10 cigarettes per day	316.7	48.2	86.0	48.3	67.0	3.7
315 men who smoke 10 19 cigarettes per day	352.2	47.1	91.7	50.2	69.6	12.7
673 men who smoke more than 20 cigarettes per day	361.5	50.2	93.1	49.3	71.1	22.6
217 men who had given up cigarette smoking	320.7	47.3	87.8	52.8	66.8	0
126 men who smoked pipes or cigars or both, but no cigarettes	335.7	48.0	90.6	59.6	68.4	0
WOMEN (Category and Number of Women)						
128 women who never smoked	303.0	32.7	51.7	14.6	48.5	0
33 women who smoke fewer than 10 cigarettes per day	299.9	30.7	49.7	14.1	47.3	4.5
66 women who smoke between 10 and 19 cigarettes per day	318.8	36.1	51.1	12.1	49.6	12.1
43 women who smoke more than 20 cigarettes per day	325.0	39.4	47.7	10.3	49.3	21.0
13 women who had given up cigarette smoking	275.7	29.8	46.6	15.0	43.9	0

* Since the mean age of the various groups of men ranged from 32.6 to 36.3 years, all values were adjusted to 35.0 years. Similarly, for women all values were adjusted to 30.0 years.

and in atherogenic index value. To be sure there does exist the *possibility* that persons of certain metabolic types or personality types may smoke more cigarettes than others and may show higher atherogenic index values than others and that the observed association of cigarette smoking with atherogenic index simply reflects such personality and metabolic types. But the existence of this as a *possibility* does not make it the *reality* hoped for by some, for it is at least equally likely (and from additional evidence much more than equally likely) that cigarette smoking *causes* the observed elevation in s_f0-12 and s_f20-100 lipoproteins

FILTER-TIP CIGARETTES VERSUS REGULAR CIGARETTES

The tobacco industry has put a great deal of effort into a campaign to induce cigarette smokers to switch to filter-tip cigarettes. There can be little doubt but that the individual smoker who chooses a filter-tip cigarette is influenced to do so by his hope that any potentially adverse effects of cigarette smoking upon health may be mitigated through the use of filter-tip cigarettes. It is of interest, therefore, to know whether or not filtering smoke through the commonly available filter tip cigarettes alters in any way the association of cigarette smoking with serum lipoprotein and atherogenic index values. The questionnaires utilized in the above-described study specifically requested information concerning the brand of cigarette smoked and whether or not the cigarette was of a filter-tip type. For purposes of analysis all non-filtered brands are considered here as one group, all filtered brands as another group. While this does not allow comparison of possible efficiency of one filter-tip with another, it does provide a measure of the effect of filtration in the form utilized by a reasonable cross-section of cigarette smokers. The comparison data are presented in Table XL No significant differences in lipoprotein levels or atherogenic index values can be demonstrated between those cigarette smokers using the usual group of filter-tip cigarettes and those using the unfiltered brands. With respect to that part of the association of cigarette smoking and coronary heart disease that arises through the association of cigarette smoking with Atherogenic Index val-

TABLE XL

Serum Lipoprotein Levels and Atherogenic Index Values in Smokers of Filter-Tip Cigarettes Versus Smokers of Regular (Non-filtered) Cigarettes*

Category	Mean S_f 0 12 mg/100ml	Mean S_f 12 20 mg/100ml	Mean S_f 20 100 mg/100ml	Mean S_f 100-400 mg/100ml	Mean Atherogenic Index (units)	Mean Number of Cigarettes Per Day
254 men who smoked filter-tip cigarettes	364.4	48 8	93 6	54.2	70 9	18.2
833 men who smoked regular (non-filtered) cigarettes	365 6	50 8	94 5	49.1	70 6	18 0

* The question concerning filtration was introduced into the latter half of this study. Hence data are available only for 1087 men for this feature. No conceivable bias was introduced by this.

ues, no amelioration of the situation is achieved by a substitution of the filter-tip cigarettes in common use during the 1954-1957 period when this study was done.

PIPE AND CIGAR SMOKING AND SERUM LIPOPROTEINS

Hammond and Horn's report on the association of smoking with coronary heart disease showed a much more striking effect for cigarette smoking than for cigar and pipe smoking, although a low degree of association could be demonstrated for cigar and pipe smoking. The data of Table XXXIX indicate that no significant elevation of any of the lipoproteins or of the atherogenic index was demonstrable in those who smoked cigars and/or pipes but who never had smoked cigarettes. Some possible explanations of the lack of an effect of the use of tobacco in these forms are: (1) a lesser consumption of tobacco in pipe or cigar smokers than in cigarette smokers, (2) a temperature difference in the burning of tobacco in the various forms, or (3) an influence of some component of cigarettes other than the tobacco itself.

REVERSIBILITY OF THE EFFECT OF CIGARETTE SMOKING UPON SERUM LIPOPROTEIN LEVELS

Many of the individuals examined in this study had at one time been smokers of cigarettes but had for a variety of reasons made the decision to quit smoking. Some had quit as recently as a few weeks before the questionnaire and blood sampling, others as long as 10 years before. An analysis was made of the lipoprotein levels of this entire group of 217 quitters of cigarette smoking in comparison with those who never had smoked cigarettes. The data are presented in Table XXXIX No significant difference in level of any of the four classes of lipoproteins or of the atherogenic index can be demonstrated to exist between the group who had quit cigarette smoking and the group who had never smoked cigarettes. If it is assumed that while the members of the first group *had* smoked cigarettes they would have shown the elevation in lipoprotein levels characteristic of

current cigarette smokers, it follows that cessation of cigarette smoking has resulted in a *reduction* in lipoprotein and Atherogenic Index values This would indicate that *whatever* the mechanism is by which cigarette smoking becomes related to elevation of blood lipoprotein levels, it is possible to overcome such elevation by cessation of smoking.

The possibility exists, of course, that the "quitters" of cigarettes represent a special group of persons among the smokers, and that the very fact that they quit smoking "proves" this The argument could be advanced that possibly *these* cigarette smokers never had had the lipoprotein elevation characteristic of cigarette smokers and hence that the absence of an elevation in quitters does not prove *reversibility* of an effect of cigarettes on serum lipoproteins. Such requirements of special types of persons, first, to explain the lipoprotein elevation in cigarette smokers, and next, to explain the effect of cessation of smoking begin to multiply the number of metabolic or personality make-ups required and render such *possible* explanations of all the findings very remote in comparison with the more plausible one that cigarette smoking is a causative agent in lipoprotein elevation and that, hence, removal of the causative influence removes the effect, as has been experimentally observed

CIGARETTE SMOKING AND BLOOD PRESSURE LEVELS

Physiologists and pharmacologists have long been interested in the possible influence of tobacco and some of its chemical constituents upon such vital measurements as the blood pressure level Many of the studies that have been reported have focussed upon the relatively acute effects of smoking upon the blood pressure Such information is extremely useful, but needs supplementation by studies of possible chronic effects of cigarette smoking upon the habitual blood pressure of individuals.

In direct investigations of the acute effect of cigarette smoking upon the diastolic blood pressure level of habitual smokers Roth[69] found that her subjects showed an average rise in diastolic pressure of 14 mm Hg above a baseline average value of 69 mm Hg during the actual act of smoking two regular cigarettes con

ues, no amelioration of the situation is achieved by a substitution of the filter-tip cigarettes in common use during the 1954-1957 period when this study was done.

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sustained effect of habitual cigarette smoking upon blood pressure level exists.

QUANTITATIVE EVALUATION OF THE RELATIONSHIP OF CIGARETTE SMOKING WITH INCIDENCE RATE OF CLINICAL CORONARY HEART DISEASE

The objective of determination of the presence or absence of an intrinsic, independent effect of cigarette smoking per se upon coronary heart disease can now be realized. First, it is necessary to assess what part of the overall effect can be explained both through the association of cigarette smoking with atherogenic index values and through that of cigarette smoking with blood pressure levels. The statistical calculations of Hammond and Horn[70] showed that regular smokers of 40 cigarettes per day (2 packs) show approximately 2.2 times as high an incidence rate of clinical coronary heart disease as do non-smokers. From the direct measurements of the relationship of cigarette smoking with lipoprotein level and atherogenic index values, smokers of 40 cigarettes per day experience an average elevation in Atherogenic Index value of 8.3 units. For men in the 40-59 year age bracket, this would mean an Atherogenic Index value of approximately 83.8 units for smokers of 40 cigarettes per day contrasted with a value of 75.5 units for non-smokers. Reference to Table XVI (Chapter V) indicates that the relative incidence rate of coronary heart disease for these atherogenic index values is 4.82/3.34, or a 1.44- fold increase in coronary heart disease incidence rate for smokers of 40 cigarettes per day compared with that for non-smokers. But this is the increase in expected incidence rate taking into account only the association of cigarette smoking with atherogenic index. Complete evaluation of the expected incidence rate in smokers *requires* also an accounting of the blood pressure effect.

Since the data described above show *no sustained* effect of cigarette smoking upon diastolic blood pressure level, the considerations need to deal only with the acute effects of cigarette smoking upon the diastolic blood pressure. In the chapter of this book (Chapter VII) where the relationship of age with

secutively. However, within approximately five minutes the diastolic pressure level had returned to the pre-smoking base-line value. Therefore, it is clear that, while smoking, the average cigarette smoker does experience a rise in diastolic blood pressure, *but the effect wears off very rapidly following the actual* act of smoking.

The rapid decay of the effect of smoking cigarettes upon the blood pressure does not preclude the possibility that habitual smoking of cigarettes may produce some sustained rise in diastolic blood pressure. However, direct studies of this question, reported below, indicate that no such sustained effect upon blood pressure is demonstrable. This was shown in the same group of 2201 consecutive employed persons who were questioned concerning smoking habits and whose lipoprotein levels were measured. The data relating blood pressure values to various categories of smoking habits are presented in Table XLI. Since the blood pressure measurements in this study were made at least 15 minutes after the act of smoking a cigarette in those who may have smoked prior to the medical examination, the type of acute effect found by Roth should not have influenced these observations. The absence of any demonstrable deviation in the mean diastolic blood pressure for habitual cigarette smokers contrasted with persons who had never smoked indicates that no

TABLE XLI

DIASTOLIC BLOOD PRESSURE LEVELS IN SMOKERS AND NON-SMOKERS*

Category	*Mean Diastolic Pressure*** *(mm Hg)*
486 men who never smoked	71.3
99 men who smoke fewer than 10 cigarettes per day	71.3
315 men who smoke 10 to 19 cigarettes per day	70.6
673 men who smoke more than 20 cigarettes per day	70.6
217 men who had given up cigarette smoking	70.7
126 men who smoked pipes or cigars or both, but no cigarettes	70.3

* The values of mean diastolic pressure were all corrected by the very small correction necessary to adjust to 35.0 years of age for all groups

** These pressures were taken reclining a minimum of 15 minutes after the last cigarette was smoked, if the examinee smoked at all

This means that the combined effect of elevation of atherogenic index and diastolic blood pressure leads to the prediction of a 1.8-fold incidence rate of clinical coronary heart disease in smokers of 40 cigarettes per day in comparison with non-smokers. This is to be compared with the 2.2- fold incidence rate actually observed by Hammond and Horn. It appears quite clear that the effect of cigarette smoking on coronary heart disease incidence rate is wholly, or nearly wholly explained by the elevation in atherogenic index and diastolic blood pressure in cigarette smokers There cannot be much residual independent status of cigarette smoking beyond these mechanisms.

Those who have quit cigarette smoking show a coronary disease incidence rate between those of smokers and non-smokers[70] The lipoprotein findings plus the accumulation concept for coronary disease risk predict precisely this result, if reversibility of *established* risk is not complete.

coronary heart disease incidence rate was discussed, it was pointed out that all the available evidence indicates that the blood pressure operates as an *accumulative* factor over time rather than as an instantaneous factor. Thus a particular elevation of blood pressure operating over two years would accumulate twice as much toward the risk of ultimate clinical coronary heart disease as would that same elevation in pressure operating over one year. In the absence of any information to the contrary, the most reasonable approximation to the effect of blood pressure elevation for much shorter intervals of time is to consider an accumulation proportional to the time interval involved. Thus, in this case, the knowledge exists from Roth's data[69] that the mean diastolic blood pressure is elevated 14 mm Hg during cigarette smoking. The average duration of this effect is approximately 10 minutes per cigarette. Therefore, a person who smokes 40 cigarettes per day would show such a blood pressure elevation for 40x10, or 400 minutes per day, or about 7 hours per day out of every 24 hours. *An elevation of diastolic blood pressure of 14 mm Hg for 7* hours out of 24 hours would correspond to an average elevation of pressure of 7/24 of 14, or 4.1 mm Hg spread over each day. This is the average increase in diastolic blood pressure that can be used to estimate the increase in coronary heart disease incidence rate resulting from the association of acute blood pressure rises with cigarette smoking. The average blood pressure of 40-59 year old men is 74.7 mm Hg, and with a 4.1 mm rise, the cigarette smokers would show an average pressure of 78.8 mm Hg. From Table XIV (Chapter V) this rise in diastolic blood pressure corresponds to a 3.94/3.16, or 1.25-fold increase in coronary heart disease incidence rate, which is the increased incidence rate anticipated for smokers of 40 cigarettes per day as compared with non-smokers.

The *overall* comparison of the coronary heart disease incidence rate for smokers of 40 cigarettes per day and for non-smokers is determined by multiplying the increased incidence rate due to the atherogenic index effect by that for the diastolic blood pressure effect. Therefore, the factor of 1.44 (for the atherogenic index effect) is to be multiplied by 1.25 (for the diastolic blood pressure effect), giving an overall factor of 1.80

the extent to which diabetes mellitus might predispose to excessive coronary heart disease today, it would be a matter of some urgency to know with what kind of people these past reports have been dealing. It is no less important to know today when one discusses diabetics with what type of people one is dealing. Unfortunately so many of the impressions concerning diabetes mellitus arise either from hospital statistics or clinical statistics that it is extremely difficult to know accurately the incidence of such complications as coronary heart disease in the diabetic population as a whole rather than in some select part of the diabetic population which finds itself going to a clinic or a hospital. This very fact alone may bias the data such as to lead to an erroneous impression concerning complications of the diabetic state. A variety of complaints may ultimately lead a person with a disease such as diabetes mellitus to seek care in a medical clinic, one of which complaints might be angina pectoris or other manifest coronary heart disease. Hence, the analysis of hospital statistics or clinic statistics with respect to the incidence of coronary heart disease in diabetes mellitus may be grossly misleading as an index to the status of diabetics in the population-at-large. Perhaps the most effective way to start consideration of this problem is to look back at the pre-insulin period In the pre-insulin period we had what might be called essentially a homogeneous population of diabetics at least with respect to the one fact that none of them were being treated with insulin, which can no longer be said at the present time. During that period it appears reasonably certain that coronary heart disease and sequelae of arteriosclerosis in other vascular beds was more frequent in the diabetic subjects than in the population-at-large. Even during that period the estimate of the frequency of such disease in the diabetics must have been biassed by the fact that certainly the more severe cases and those with complications most readily found their way into the hospital and clinic populations from which coronary disease statistics were derived for the diabetic Still, for the [illegible] period, we can look [illegible] concerning such pati[illegible] what might have been expected then with respect to coronary heart disease.

Chapter XII

THE RELATIONSHIP OF DIABETES MELLITUS WITH CORONARY HEART DISEASE

THE OPINION *is still widely held in medical circles that* diabetes mellitus is a disorder characterized by an excessive incidence of premature coronary heart disease. Indeed it has often been stated by medical authorities that, since diabetes mellitus *itself need no longer be a fatal disease because of the use of* insulin or some of the recent substitutes for insulin therapy, the diabetic now dies of the complications of arteriosclerosis, among which coronary heart disease is prominent. The crucial question at hand is "*To what extent does the diabetic die of coronary heart* disease earlier in life than does any member of the population-at-large? If the diabetic is protected against death from diabetic acidosis and coma and therefore becomes essentially a member *of the population-at-large (but with diabetes), one could anti*cipate that coronary heart disease may be at least as frequent among diabetics as it would be among other members of the population. Since coronary heart disease occurs so frequently in the popula*tion-at-large, it is not surprising that physicians should run into* many diabetics who develop coronary disease, ultimately including between ¼ and ½ of them. But if this frequency of heart disease is no greater in diabetics than in the population-at-large, then *the impression that diabetes mellitus is a predisposing* factor *as of today,* might be erroneous.

Oft quoted in support of the concept of the excessive frequency of coronary heart disease in diabetes mellitus are data published *in the literature between 1930 and 1950* and based upon the consideration of persons who were in their sixties and seventies during that period. Before reaching a conclusion as to

the extent to which diabetes mellitus might predispose to excessive *coronary heart* disease today, it would be a matter of some urgency to know with what kind of people these past reports have been dealing. It is no less important to know today when one discusses diabetics with what type of people one is dealing. Unfortunately so many of the impressions concerning diabetes mellitus arise either from hospital statistics or clinical statistics that it is extremely difficult to know accurately the incidence of such complications as coronary heart disease in the diabetic population as a whole rather than in some select part of the diabetic population which finds itself going to a clinic or a hospital. This very fact alone may bias the data such as to lead to an erroneous impression concerning complications of the diabetic state. A variety of complaints may ultimately lead a person with a disease such as diabetes mellitus to seek care in a medical clinic, one of which complaints might be angina pectoris or other manifest coronary heart disease. Hence, the analysis of hospital statistics or clinic statistics with respect to the incidence of coronary heart disease in diabetes mellitus may be grossly misleading as an index to the status of diabetics in the population-at-large. Perhaps the most effective way to start consideration of this problem is to look back at the pre-insulin period In the pre-insulin period we had what might be called essentially a homogeneous population of diabetics at least with respect to the one fact that none of them were being treated with insulin, which can no longer be said at the present time. During that period it appears reasonably certain that coronary heart disease and sequelae of arteriosclerosis in other vascular beds was more frequent in the diabetic subjects than in the population-at-large. Even during that period the estimate of the frequency of such disease in the diabetics must have been biassed by the fact that certainly the more severe cases and those with complications most readily found their way into the hospital and clinic populations from which coronary disease statistics were derived for the diabetic. Still, for the untreated diabetic, during the pre-insulin period, we can look at some of the scientific clinical evidence concerning such patients to determine what might have been expected then with respect to coronary heart disease.

During the pre-insulin period the availability of therapy other than dietary therapy was essentially non-existent, and during that same period uncontrolled diabetes can be said to have been rampant. To be sure, the obese middle-aged diabetic during that period was in essence no different from the obese middle-aged diabetic of today. We do know that in such cases of diabetes that the correction of diet and of attendant overweight will in many cases lead to an amelioration of the diabetic state, a reduction in, or elimination of, glycosuria, a reduction in hyperglycemia, and clinical well-being wholly without the use of insulin. However, there were many diabetics in whom this favorable set of changes could not be induced by dietetic therapy alone during the period in which insulin was absent from the scene. The occurrence of episodes of severe acidosis and even of coma was a frequent occurrence, with a large number of diabetics dying during such episodes. Diabetic acidosis of severe degree and diabetic coma still occur today although much more infrequently than before, but nevertheless their occurrence provides us with a direct way of observing the type of phenomenon that must have been extremely common during the pre-insulin period. Among the most startling findings in uncontrolled diabetes in acidosis or in coma are those which center around the alterations of blood lipid transport. Indeed it can be stated that no other disease has yet been observed which is capable of producing within a matter of days the massive changes in blood lipid transport that can be observed as a diabetic patient passes from control into decontrol and acidosis, and conversely as a diabetic in coma or acidosis is once more brought under control. These considerations can best start with the diabetic in severe decontrol and acidosis with or without coma Numbers of these patients have been studied with respect to the lipoprotein levels of the various classes involved in coronary heart disease, such as the s_f0-12, s_f12-20, s_f20-100, and s_f100-400 classes, during the phase of severe diabetic acidosis and decontrol and during the phases of return to control[71, 72].

The average patient under these circumstances is characterized by a very, very marked derangement of blood lipoprotein transport which involves a lowering of the s_f0-12 lipoproteins,

TABLE XLII

SERUM LIPOPROTEIN LEVELS IN DIABETIC ACIDOSIS AND COMA

Case	Age (years)	Sex	Clinical State	S_f0-12 mg/100ml	S_f12-20 mg/100ml	S_f20-100 mg/100ml	S_f100-400 mg/100ml	Atherogenic Index (units)
1	37	F	Marked Acidosis No coma Cutaneous Xanthomata	195	155	1120	3739	897
2	44	F	Acidosis and Coma	172	65	343	383	156
3	55	F	Acidosis No coma Cutaneous Xanthomata	235	54	1082	1622	506
4	21	M	Acidosis Semi coma	74	9	334	865	219
5	11	F	Acidosis Semi coma	0	0	416	700	195
6	21	F	Acidosis No coma	179	81	656	647	260
7	39	F	Acidosis Coma	408	139	264	291	162
8	35	M	Acidosis Semi coma	101	40	20	7	52
9	52	F	Acidosis No coma	356	105	164	72	95
10	13	F	Acidosis No coma	226	91	105	51	63
Grand Mean for 10 cases				224.6	74.2	450.4	835.7	260.5

accompanied by a massive elevation of the lipoproteins of higher flotation classes, including those of the s_f20-100 class, the s_f100-400 class, and lipoproteins of even higher classes all the way out to those known as chylomicrons. In Table XLII are presented the initial findings available for a series of diabetics who were in the hospital in severe acidosis with or without coma. It can be noted that 7 out of 10 of these patients showed a marked derangement in lipoprotein transport of the type just characterized. The mean values of the four lipoprotein classes for all ten cases shows the marked depression in s_f0-12 lipoproteins and the massive elevation of the s_f20-100 and s_f100-400 lipoprotein classes. While every diabetic in acidosis does not show a marked derangement of lipoprotein levels, the averages and the distribution of values speak for themselves with respect to the tremendous derangement that can be said to characterize the usual state of diabetic acidosis and severe diabetic decontrol. The average Atherogenic Index value of 260.5 units is between 3 and 4 times the average for adult males or females in the population-at-large. Hence, with respect to the *rate of accumulation* of sub-clinical coronary heart disease (in all probability in the form of an increment in narrowing of the coronary arteries) it can be expected that the average diabetic in the state of acidosis is accumulating sub-clinical coronary heart disease at a phenomenal rate During the pre-insulin period many diabetics probably could not have chronically been this far out of control, but undoubtedly many of them must have been oscillated into and out of states approaching this degree of decontrol. It would be anticipated that during such phases of decontrol they were developing an extensive degree of sub-clinical coronary heart disease It is not necessary for diabetics to be in a state of coma or semi-coma in order to show the marked derangement in lipoprotein levels which accompanies severe diabetic decontrol. Illustrative changes in lipoprotein levels for one patient followed carefully during her hospital stay while the diabetes was being brought under control are presented in Table XLIII.

A most interesting sequence of events is observed during the period of days, weeks and months during which the diabetic patient has been brought under control from the state of severe

TABLE XLIII

Serial Lipoprotein Studies During the Therapy of Diabetic Acidosis in a 37 Year Old Patient

Day After Hospital Admission	Clinical State	S_f0-12 mg/100ml	S_f12 20 mg/100ml	S_f20-100 mg/100ml	S_f100-400 mg/100ml	Atherogenic Index (units)
0	In acidosis and coma	195	155	1120	3739	897
4th day	Out of acidosis	441	352	1912	1530	714
9th day	In diabetic control	744	428	1277	685	493
14th day	In diabetic control	939	338	670	139	295
29th day	In diabetic control	614	131	493	228	211
43rd day	In diabetic control	531	148	432	132	178
50th day	In diabetic control	616	150	332	152	173
56th day	In diabetic control	549	108	150	51	105
—Discharged from hospital—						
116th day	Supposedly in diabetic control at home but showing acetonuria	452	237	988	461	340
400th day	Supposedly in diabetic control at home but showing acetonuria	276	188	968	840	377

diabetic acidosis. As the diabetes is brought under control through usual medical measures, including insulin among others, the massively elevated levels of lipoproteins above s_f400 and of the s_f100-400 class are noted to decline as a very early phenomenon. During the time when the levels of these lipoproteins are falling, there is first a rise in concentration of those of successively lower flotation classes. Thus, as the s_f100-400 lipoprotein levels start falling, the s_f20-100 lipoprotein levels show a rise in concentration, as though there might actually be a transformation occurring from the lipoproteins of the higher flotation classes to those of successively lower flotation classes. With the passage of a little more time measured in days the s_f100-400 lipoprotein levels fall still further and then the s_f20-100 lipoprotein levels, which at first were rising, begin to decline, accompanied first by an increase in the s_f12-20 lipoproteins and finally also in the s_f0-12 liproproteins. Still further along in this entire evolutions of events the s_f20-100 and s_f100-400 lipoproteins may approach values of the order of these observed in the population-at-large (even lower than for many persons in the population-at-large). At this time the s_f0-12 lipoprotein levels are massively elevated in comparison with the levels encountered in the members of the population-at-large. Finally, with further maintenance of diabetic control, the massive elevation of the s_f0-12 lipoprotein levels recedes, leaving the diabetic ultimately with the type of pattern that characterizes him or her during a state of control. The lipoprotein distribution in diabetic control is not a standard one, since there is variability among diabetics in control just as there is variability in the levels of the various lipoprotein classes among the members of the population-at-large All the events described above have been observed in several diabetic patients going from the stage of severe acidosis and decontrol back to control, so that it is by no means the happenstance of a single, particular diabetic patient. This sequence of changes can be regarded as a general trend which characterizes diabetes during these stages Furthermore, certain patients who have been brought out of severe acidosis have been observed for a period of months and years while attempting to control their diabetes at home. The patient described in Table XLIII was observed

during a repeat episode of acidosis (although clinically a much milder episode of acidosis than during the initial study). During this second, relatively mild episode of acidosis the patient showed a reversion to a lipoprotein distribution intermediary between that observed in the earlier marked decontrol stage and that in the stage of control during her hospital stay. This general train of events can be anticipated to have been extremely common during the period before the introduction of insulin, even though lipoprotein values were not available during that time to delineate the changes

That a disease process such as the accumulation of subclinical coronary heart disease was, in all probability, going on excessively during such a period is supported by auxiliary (though not necessary) evidence concerning the development of xanthomatosis in the diabetic patient. Xanthoma diabeticorum, which is more commonly referred to as *eruptive* xanthoma diabeticorum is a lesion occurring in the skin histopathologically closely akin to the arterioatherosclerotic lesions of the coronary artery and of other medium and large arteries There are pathologists who would claim the ability to distinguish a xanthomatotic lesion from an athero-arteriosclerotic lesion even though both lesions are grossly similar. One might question the ability to make this distinction if the surrounding landmarks of tissue such as the coats of the vessel in the case of the arteriosclerotic lesion or the overlying skin in the case of the skin lesion were stripped away leaving the bare lesion Under these circumstances it can be fairly well assured that pathological differentiation of the lesions would be much less readily made There are abundant reasons to consider that the pathogenesis of these two lesions is extremely similar. Diabetic patients do not commonly show the lesion of eruptive xanthoma diabeticorum during diabetic control. Indeed the very term, eruptive, indicates the relatively acute onset of development of such lesions and the acute nature of the entire process These lesions erupt during some aspect of the phase of severe diabetic decontrol and acidosis and may persist and increase during the stage of marked diabetic acidosis and coma It is to be noted that such lesions occur in those cases who have enormously elevated lipoprotein levels of the S_f12-400 class as part of their

manifestation of the entire phenomenon of diabetic acidosis and decontrol. There is very little doubt that the massively elevated lipoprotein levels of these classes are directly associated with the development of the eruptive xanthoma diabeticorum. Furthermore, as the diabetic is brought back into control, and out of acidosis, and as the lipoprotein levels recede toward much more normal levels, the lesions of xanthoma diabeticorum no longer develop de novo. Old lesions, which had appeared during the stage of massive lipoprotein elevation, begin to decrease in size, and in a period of weeks and months, trailing the lipoprotein level lowering, the lesions generally disappear completely, leaving in most areas very little if any trace of the xanthomata. This xanthomatous lesion, which develops in association with extremely high lipoprotein levels, is a manifestation of what can happen in the skin if lipoprotein levels are high enough. For a process such as this it appears unquestionable from a variety of types of evidence that certain regions of the body differ with respect to receptivity to formation of the lipid-filled lesions of this character. It is not surprising, therefore, to find that skin may be one of the less receptive areas as compared with tissues in general, such as arterial walls, and that the lesions which are seen in the skin form only when the lipoprotein levels are massively elevated There is no reason to consider that the lipoproteins are different in kind from those which exist at lower levels in the population-at-large, but rather that they are so massively elevated in concentration during the state of diabetic acidosis that the skin lesions form The corresponding arterial lesions we can feel quite certain form at much, much lower lipoprotein levels in the blood since arteriosclerosis proceeds at a fair rate in the population-at-large with more moderate lipoprotein levels

Thus, during a phase of diabetic decontrol and acidosis with its massive elevation of lipoprotein levels, it can be anticipated that, whatever rate of coronary atheroma development usually existed in such an individual, it will have been massively accelerated during the periods of decontrol with the fabulous rises in lipoprotein levels which accompany such periods. The diabetic during the pre-insulin period must have been in and out of phases of severe acidosis and may have been midly acidotic for

very long periods of time, since full control of the diabetes was not possible in that era without the assistance from insulin therapy. Therefore regression of arteriosclerotic lesions that might have occurred (analogous to the regression of the xanthomatous lesions which occurs when the lipoproteins are lowered in an acidotic diabetic), may have been inhibited because of the maintenance of mild acidosis. From studies of other xanthomatoses, such as xanthoma tuberosum, it is known (see Chapter X) that the longer standing lesions are no longer primarily the lipid-laden lesions, but instead have accumulated a considerable amount of fibrous tissue. During the regression of such longer-standing lesions in xanthoma tuberosum which accompanies lowering of lipoprotein levels, the lipid element of the lesion regresses very markedly and may disappear entirely, but the fibrous element does not To what extent the fibrotic element in the arteriosclerotic lesion develops more rapidly or less rapidly than in the xanthomatotic lesion cannot be stated, but it is certain to develop at some reasonably comparable pace. Therefore, for the diabetic who has spent a fair part of his life in the acidotic state, or decontrol state, there will be expected, with each deposition of lipid in arterial lesions, a development of fibrosis and hence some accumulation of a partially or wholly irreversible part of the lesion even though the diabetes has been brought under control by medical measures.

The entire discussion of the xanthomatosis of diabetes, its relationship with the arteriosclerotic lesion, and the relationship of both of these with the progression of sub-clinical coronary heart disease in patients with diabetes is *ancillary* evidence As stated earlier in this book, because of controversies concerning the primacy of events in the development of the arteriosclerotic lesion, evidence pertaining to arteriosclerosis would not be utilized as basic support for demonstration of the factors involved in the development of sub-clinical and clinical coronary heart disease. However, where ancillary evidence deriving from pathology might help understand a particular issue, such ancillary evidence should not be neglected. In this case there exists no need to utilize the ancillary evidence as the basic proof or evidence for the phenomenon at hand, but it does lend further consistency to

manifestation of the entire phenomenon of diabetic acidosis and decontrol. There is very little doubt that the massively elevated lipoprotein levels of these classes are directly associated with the development of the eruptive xanthoma diabeticorum. Furthermore, as the diabetic is brought back into control, and out of acidosis, and as the lipoprotein levels recede toward much more normal levels, the lesions of xanthoma diabeticorum no longer develop de novo. Old lesions, which had appeared during the stage of massive lipoprotein elevation, begin to decrease in size, and in a period of weeks and months, trailing the lipoprotein level lowering, the lesions generally disappear completely, leaving in most areas very little if any trace of the xanthomata. This xanthomatous lesion, which develops in association with extremely high lipoprotein levels, is a manifestation of what can happen in the skin if lipoprotein levels are high enough. For a process such as this it appears unquestionable from a variety of types of evidence that certain regions of the body differ with respect to receptivity to formation of the lipid-filled lesions of this character It is not surprising, therefore, to find that skin may be one of the less receptive areas as compared with tissues in general, such as arterial walls, and that the lesions which are seen in the skin form only when the lipoprotein levels are massively elevated. There is no reason to consider that the lipoproteins are different in kind from those which exist at lower levels in the population-at-large, but rather that they are so massively elevated in concentration during the state of diabetic acidosis that the skin lesions form. The corresponding arterial lesions we can feel quite certain form at much, much lower lipoprotein levels in the blood since arteriosclerosis proceeds at a fair rate in the population-at-large with more moderate lipoprotein levels.

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showing effects upon their coronary heart disease risk due to the time they spent as diabetics during the pre-insulin period. This point is commonly overlooked by authors writing in the 1940's and 1950's, especially concerning diabetics in the seventh, eighth, and ninth decade of life and their incidence of coronary and other vascular disease. Such evidence can hardly be utilized to provide the requisite information concerning the fate of diabetes of today under good control. Therefore it is necessary to reevaluate completely for the diabetic of the present era what the real situation is with respect to the incidence of coronary heart disease.

THE INCIDENCE OF CORONARY HEART DISEASE IN DIABETES MELLITUS IN THE POST-INSULIN PERIOD

Ideally, the determination of any possible increase in incidence rate of clinical coronary heart disease in diabetics during the post-insulin period would require the following evaluations:

(1) The real incidence of diabetes mellitus in the population-at-large at various ages and for both sexes
(2) Follow-up observations of an adequately large series of such diabetics, random in the population-at-large, to determine the age specific incidence rate of clinical coronary heart disease for both sexes
(3) Follow-up of an adequately large sample of the non-diabetic population-at large to determine the age-specific incidence rate of clinical coronary heart disease in both sexes.
(4) Assurance that the diabetic persons had not spent a large share of their life in the pre-insulin era This would not be a serious problem in data collected now, although it certainly has been in literature reports of the past few decades

What is available now in the way of evidence falls short by a tremendous margin of such evaluations. The pitfalls of utilization of clinic or hospital patients or of hospital autopsy data are many and have been alluded to in the earlier discussion above Thus comparison of the frequency of occurrence of diabetes mellitus in a hospital series of myocardial infarctions with the prevalence of diabetes in an age and sex-matched sample of the

the concepts involved. All the evidence concerning diabetic acidosis is self-sufficient in terms of the direct relationship of blood lipoproteins to the development of sub-clinical coronary heart disease without the intermediacy of the arteriosclerotic or xanthomatotic lesions. Since it has been shown before (see Chapter V) that the higher the lipoprotein level, the greater is the accumulation rate of sub-clinical coronary disease, and hence *the greater ultimate risk of clinical coronary disease, it can be* stated that a diabetic in acidosis, with the lipoprotein levels which characterize that state, would have been accumulating sub-clinical coronary heart disease at a tremendously increased rate in comparison with the diabetic in control or with the non-diabetic. Hence the frequent existence of severe decontrol of diabetes during the pre-insulin period should have markedly increased the predisposition of diabetic patients to the development of early and severe coronary heart disease. This is completely consistent with the numerous literature reports of a high incidence of coronary heart disease in the pre-insulin period. *However, the pre-insulin period is over* Indeed, we are in a phase now where insulin itself is being compared with numerous other drugs that may replace it in part at least in the management of certain diabetic patients All the considerations of coronary heart disease incidence rate for the pre-insulin period, with its high frequency of acidosis and coma, are of very little moment for the present era. The crucial question is whether or not diabetes as it is usually encountered today is still characterized by any excessive frequency of coronary heart disease In order to assess this issue critically several points must be carefully considered First, when statistical data concerning the incidence of coronary heart disease in diabetic patients between 1930 and 1950 are reviewed, it must be remembered that many of such diabetics (especially those in the older age groups) must have spent a considerable portion of their life in the pre-insulin period or in the early insulin period when insulin was not as widely used as it has been in more recent years. Hence, if at least *part* of the accumulation of sub-clinical coronary heart disease is not reversible, it would be expected that some of the diabetics of the 1930-1950 era, especially those of older age groups, would still be

showing effects upon their coronary heart disease risk due to the time they spent as diabetics during the pre-insulin period. This point is commonly overlooked by authors writing in the 1940's and 1950's, especially concerning diabetics in the seventh, eighth, and ninth decade of life and their incidence of coronary and other vascular disease. Such evidence can hardly be utilized to provide the requisite information concerning the fate of diabetes of today under good control. Therefore it is necessary to reevaluate completely for the diabetic of the present era what the real situation is with respect to the incidence of coronary heart disease.

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(3) Follow-up of an adequately large sample of the *non*-diabetic population-at-large to determine the age-*specific incidence* rate of clinical coronary heart disease in both sexes.

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What is available now in the way of evidence falls short by a tremendous margin of such evaluations The pitfalls of utilization of clinic or hospital patients or of hospital autopsy data are many and have been alluded to in the earlier discussion above. Thus comparison of the frequency of occurrence of diabetes mellitus in a hospital series of myocardial infarctions with the prevalence of diabetes in an age and sex-matched sample of the

non-diabetic population can be seriously biassed. For example, a hospital with a well-known and well-managed diabetes clinic service is likely to have a higher proportion of diabetics in its overall clientele than characterizes the incidence of diabetes mellitus in the population-at-large. In such a clinic there will exist a high index of awareness of coronary heart disease among their diabetics. This together with the loading of the overall clientele with diabetics will tend to produce a falsely high incidence of diabetes mellitus in a myocardial infarction series from such a hospital, if that incidence of diabetes is compared with the incidence of diabetes in the population-at-large. Similarly, if a hospital draws upon one group, ethnically or on some other basis, the incidence of diabetes in a myocardial infarction series cannot and should not be justifiably compared with that in the population-at-large. It has been stated in the literature[73] that Jews show a higher prevalence of diabetes mellitus than that for the non-Jewish population. If this be true, it is completely inappropriate to relate the incidence of diabetes in a series of myocardial infarction cases from a Jewish hospital with the incidence of diabetes mellitus in the overall population-at-large.

A survey of the litereature (even avoiding those reports contaminated by diabetics from the pre-insulin period), reveals that the possibilities for bias are large and, unfortunately, subtle enough that efforts to correct for such bias are not particularly fruitful.

However, even with whatever bias exists in the literature reports from clinics and hospitals, it is not unreasonable to try to establish some upper limits to any excessive predisposition of diabetic persons to develop clinical coronary heart disease utilizing such literature data The nature of the biassing errors are in general such as to *overestimate* any excessive risk for diabetics rather than to underestimate it. Wright et al, Master et al, Doscher and Poindexter, and Mintz and Katz have provided data concerning the prevalence of diabetes mellitus among myocardial infarction cases both for their own series and from the literature[24, 74, 28, 29]. These prevalence data are reproduced below

	Males	*Females*
Wright, Marple and Beck	7.1% (Based upon 774 cases)	21.2% (Based upon 210 cases)

Doscher and Poindexter	5.1% (Based upon 351 cases)	18.9% (Based upon 80 cases)
Master, Dack and Jaffe	6.7% (Based upon males among 550 cases)	26.0% (Based upon 150 cases)
Mintz and Katz	9.2% (Based upon 392 cases)	27.2% (Based upon 180 cases)
Total cases	1830	650

The best prevalence from all these data is the weighted mean values for all the series, which yields the values, 7.1% of men with myocardial infarction are diabetics and 24.8% of women with myocardial infarction are diabetics. The mean age of such infarction series is approximately 60 years.

From the systematic community study at Oxford, Massachusetts by Wilkerson and Krall[75], the prevalence rates of diabetes mellitus in a population sample at comparable mean ages were:

For men at 60 years of age, 5.2% of the population sample was diabetic
For women at 60 years of age, 7.2% of the population sample was diabetic.

Suppose that the male diabetic at 60 years of age is more prone to develop myocardial infarction than the average male of 60 years of age in the population-at-large. We may set the risk of the diabetic male at x times that of the non-diabetic male. For every case of myocardial infarction per 1000 non-diabetic men, there would be x cases per 1000 diabetic men of the same age. With this information, the data above concerning the incidence of diabetes in 60 year old men in the population-at-large, and the incidence of diabetes in the myocardial infarction series, the value of x can be calculated. The observed ratio of male non-diabetic myocardial infarction cases to diabetic myocardial infarction cases is 92.9 to 7.1. In the population-at-large there would be 5.2 diabetic men for every 94.8 non-diabetic men. Whatever the incidence rate of myocardial infarction is in non-diabetic men, the rate for diabetic men has been set at x times that value. Therefore the number of cases of myocardial infarction arising from the non-diabetic men is (94.8) times (the incidence rate). Out of the same 100 men, the number of cases of myocardial infarction arising from the diabetic men is (5.2) times (the incidence rate) times (x). The ratio of non-diabetic infarction cases to diabetic infarction cases is therefore=

$$\frac{(94.8)\text{ times (Incidence Rate)}}{(5.2)\text{ times (Incidence Rate) times (x)}}$$

The (incidence rate) factor cancels out in this ratio, leaving 94.8 over (5.2) times (x). But this must be set equal to the observed ratio of 92.9 over 7.1. Therefore:

$$\frac{94.8}{5.2x} = \frac{92.9}{7.1}$$

Solving, it is found that:

$$x = \frac{(94.8)\ (7.1)}{(92.9)\ (5.2)} = \frac{673}{483} = 1.39$$

Therefore, it turns out that, even utilizing data which may be biassed toward overstating the hazard of coronary heart disease in diabetics, the diabetic man at an average age of 60 years *is only 1.39 times as likely to develop coronary heart disease* as is the non-diabetic man of the same age.

In an entirely analogous manner the risk of the diabetic women of 60 years compared with the non-diabetic women is calculated. Here, we have:

$$\frac{75.2}{24.8} = \frac{92.8}{7.2x}, \text{ or } x = \frac{(92.8)\ (24.8)}{(75.2)\ (7.2)} = \frac{2301}{541} = 4.25$$

Therefore, the diabetic woman at age 60 years has approximately 4.3 times the risk of coronary heart disease compared with the non-diabetic woman of the same age. It does appear, even allowing for bias, that there really is an appreciably excessive coronary heart disease risk in the 60 year old diabetic woman compared with the woman of the same age in the population-at-large.

IS DIABETES MELLITUS AN INDEPENDENT FACTOR IN DETERMINATION OF CORONARY HEART DISEASE RISK?

Diabetes mellitus is no exception to what must be our general approach to the evaluation of factors associated with coronary heart disease, namely a determination of whether it operates as an *independent, or new,* factor or whether it operates through one of the two basic known factors, the Atherogenic Index, the diastolic blood pressure, or both. Clinically and practically the answer to this question is of vast importance to the physician and to every person who has diabetes mellitus. For, few issues are more crucial than to know whether *anything*

about diabetes per se is involved in acceleration of the development of sub-clinical coronary heart disease. If not, new vistas open both for the physician and the diabetic patient for whom he is the medical counselor.

Evaluation of the extent to which diabetes mellitus may predispose to coronary heart disease through elevation either of Atherogenic Index or diastolic blood pressure, or both, requires some knowledge of the values of these variables in cross-sections of *today's* diabetics Hypertension and overweight are known to be common findings in the older diabetic woman especially, and there is good literature documentation of these findings. The hypertension would itself be a predisposing factor, and the overweight is known from independent studies to be associated with atherogenic index elevation. However, direct data in diabetic persons are still vital. In the course of a large-scale evaluation of lipoprotein levels as a predictive indicator for coronary heart disease (Table IV), the Donner Laboratory studied bloods from several thousand persons of the National Heart Institute evaluation of a cross-section of the community of Framingham, Massachusetts plus certain groups of industrial employees. There were, among these thousands of individuals, a reasonable number of diabetic persons. Of 31 diabetic females, 24 were members of the Framingham Community study, 7 were employees of the Eastman Kodak Corporation and 1 was an employee of the Los Angeles Civil Service Commission Of 69 diabetic males, 32 were members of the Framingham Community study, 20 were employees of the Eastman Kodak Corporation, 11 were employees of the Los Angeles Civil Service Commission, 5 were employees of United Air Lines Corporation and 1 was an employee of the Pan American Airlines Company Probably the overall group of diabetics is as reasonable a cross-section of diabetics as could be obtained for study, short of a mammoth effort It is certainly a better index of *the* diabetic population than a group chosen from a diabetic clinic or hospital The mean Atherogenic Index values and diastolic blood pressures for these diabetics are compared with those for their matched non-diabetic groups in Table XLIV. The elevations in Atherogenic Index for diabetic males versus non-diabetic males and for diabetic females versus non diabetic

females are appreciable and highly significant ($p<<0.01$). The blood pressure in diabetic males is only slightly above that in the non-diabetic male and cannot be proven significant. The blood pressure in diabetic women is appreciably and significantly above that for the non-diabetic women.

Risk accounting is performed in the manner described in Chapter V. For the diabetic man, the Atherogenic Index of 97.0 units (Table XVI) corresponds to a coronary heart disease risk of 7.2 times that of the reference Atherogenic Index of 30 units. For the average non-diabetic man the Atherogenic Index of 81.7 units corresponds to a risk of 4.46. Therefore the incidence rate of coronary heart disease in diabetic men of this age is expected to be 7.2 over 4.46 equals 1.61 times that for the non-diabetic man of the same age, *based upon the Atherogenic Index* alone. The blood pressure difference of 2.0 mm between diabetic and non-diabetic men was not provably significant. If it is real, then from Table XIV, the relative risk for diabetic men versus non-diabetic men (for pressures of 87.0 mm and 85.0 mm, respectively) is 5.30 over 4.98 equals 1.06. Therefore from diastolic blood pressure alone, the relative risk for diabetic men is between 1.00 and 1.06 that for non-diabetic men of the same age.

TABLE XLIV

ATHEROGENIC INDEX VALUES AND DIASTOLIC BLOOD PRESSURES IN A CROSS SECTION OF DIABETIC PERSONS AND IN GROUP-MATCHED NON-DIABETIC PERSONS

MEN (69 diabetics)	*Mean Age*	*Mean Atherogenic Index (units)*	*Mean Diastolic Blood Pressure (mm Hg)*
Diabetics	52.8 years	97.0	87.0
Matched Non Diabetic Controls	52.8 years	81.7	85.0
Difference (Diabetics - Non-Diabetics)		+ 15.3	+ 2.0
WOMEN (31 diabetics)			
Diabetics	51.5 years	98.3	93.6
Matched Non-Diabetic Controls	54.3 years	78.2	87.4
Difference (Diabetics - Non Diabetics)		+ 20.1	+ 6.2

The overall, or *net* risk, is obtained by multiplication of that from Atherogenic Index by that from diastolic blood pressure (Chapter V). The overall coronary heart disease incidence rate for diabetic men is therefore predicted to be between 1.0x1.61 and 1.06x1.61, or between 1.61 and 1.71 times as high as that for the age-matched non-diabetic man. This is to be compared with the above described observed relative incidence rates (from myocardial infarction series) of 1.39 times in diabetic men as in non-diabetic men for the same general age range This represents excellent agreement between the observed relative incidence rate and the rate predicted from the combination of Atherogenic Index and diastolic blood pressure. Considering the nature of the material available for such a study, the extent of agreement is close enough so that it can be stated that Atherogenic Index plus blood pressure effects account for the vast bulk, if not all, of the effect of diabetes mellitus in predisposing men to coronary heart disease

For the diabetic women the average Atherogenic Index of 98.3 units compared with 78.2 units for the age-matched non-diabetic women corresponds (Table XVI) to a relative risk of 7.43 over 3.84, or 1.93 times This accounts only for the contribution to risk from the Atherogenic Index For the diabetic women the average diastolic blood pressure of 93.6 mm Hg compared with 87.4 mm in age matched non-diabetic women corresponds (Table XIV) to a relative risk of 6.44 over 5.37, or 1.20 times The overall, or net risk, obtained by multiplying that from Atherogenic Index by that from diastolic blood pressure, is 1.93x1.20 = 2.31 This relative incidence rate is to be compared with that observed (myocardial infarction series) of 4.25 times. Thus, this approximate type of analysis indicates that the combination of Atherogenic Index plus diastolic blood pressure accounts for the order of 54% of the overall increased risk for diabetic women compared with non-diabetic women. When consideration is given to the sources of material and the relatively small series of diabetic women available, it is entirely possible that essentially all the excessive risk of coronary heart disease in diabetic women is accounted for by the combined effects of

Atherogenic Index and diastolic pressure. In any event it appears that these effects account for over half of the excessive risk.

These calculations indicate that for diabetics as a group the diastolic pressure and the Atherogenic Index together account for the largest share of the excessive heart disease rate experienced. If any other features of diabetes are of *any* consequence, they can at best account only for a small part of the excessive risk. There exists no valid scientific evidence in the literature to support the idea that some intrinsic feature of diabetes *per se* contributes in any way to an increased incidence rate of coronary heart disease among diabetics. Indeed no previous study has ever been reported which attempted to ascertain quantitatively whether or not the diastolic blood pressure elevation and the Atherogenic Index elevation were a sufficient basis for the excessive heart disease risk of diabetics. Speculations are rife concerning the possibility of metabolic and/or structural features surrounding capillary integrity in diabetics but no evidence whatever has come forth to show that such features are of any consequence whatever for the coronary arteries. Reference to the capillary lesions of the retina and the kidney may be wholly irrelevant to the situation in the coronary arteries. Indeed the observation of massive elevation of blood lipoproteins in diabetic retinopathy[76] and in diabetic nephropathy[77] may even suggest that the hyperlipoproteinemia should be considered as a possible contributing precursor of those capillary lesions.

The impression that diabetes *per se must* be a contributing factor to excessive risk of coronary heart disease, over and above Atherogenic Index and blood pressure effects, arises commonly from two erroneous sources. First, physicians are properly impressed that their diabetic patients do experience considerably more frequent coronary heart disease than their non-diabetic patients Often overlooked, however, is the fact that their average diabetic patient *is older* than the average person in the population-at-large. Diabetes is a disorder the incidence of which increases sharply with increasing age. Thus, even if consideration is limited to adults in the 30-69 year age range, it is readily demonstrable that the average age of men in the diabetic population is *52.5* years compared with *46.3* years for non-diabetic men,

and 53.1 years for diabetic women compared with 44.1 years for non-diabetic women. Since a 10 year difference in age would of itself lead to a tripling of the incidence rate of coronary heart disease, the fact that diabetics in our population are 6 to 9 years older than non-diabetics would itself lead to an expected rate of coronary heart disease two to three times higher in the diabetics. The way to avoid such erroneous impressions is always to compare groups on an age-specific basis, as was done in the earlier calculations of this discussion

The second erroneous source of the impression that diabetes *per se* must contribute to an excessive hazard of coronary heart disease is the expectation that diabetics would have to show the massive blood lipid elevations of the pre-insulin period. Such blood lipid elevation is *far* from necessary in order to explain excessive risk of coronary heart disease The data of Table XVI show what an increase in risk a *rise of 10* Atherogenic Index units means Such rises are not massive at all, and unless the nature of the risk tables is understood, the wrong impression will be gained Indeed, if many diabetics showed the massive blood lipid elevations expected in some quarters, their hazard of coronary heart disease would be vastly above what it now is

PRACTICAL CLINICAL IMPLICATIONS OF THE NATURE OF THE ASSOCIATION OF DIABETES MELLITUS WITH CORONARY HEART DISEASE

Since it appears that Atherogenic Index elevation and blood pressure elevations are the prime contributors to the excessive hazard of coronary heart disease in diabetic patients (as in people in general), some important features of management of the diabetic patient need discussion. These center around (1) the relationship of diabetic control to subsequent evolution of clinical coronary heart disease, and (2) prognostic information for the diabetic patient

DOES STRICT CHEMICAL CONTROL OF DIABETES MELLITUS DECREASE THE HAZARD OF CORONARY HEART DISEASE?

Emotionalism, much more than evidence, has held the stage in this question of the value of strict chemical control of diabetes mellitus for prevention of premature vascular disease. Some rational, unbiased approaches have sorely been needed in this area. Ideally it should be possible to determine the age-specific incidence rate of a complication such as coronary heart disease by observing the fate of diabetics under various types of management regimens. This, it has been shown, is easier to propose than to execute. The questions of comparability of patient material from various clinics, the many medical measures employed over and above diabetic control, and a host of other features have arisen to leave this problem largely unanswered.

It seems reasonable to state that, since lipoprotein levels, Atherogenic Index values and blood pressure together account quantitatively for most of the excessive hazard of coronary heart disease in diabetic patients, one might profitably look at the relationship of chemical control with these variables. The studies of diabetics in acidosis show a marked Atherogenic Index elevation to characterize that state. Therefore, it is quite apparent, without further evidence, that de-control of diabetes to this extent is contra-indicated, as it is on other grounds as well. But this is not the real clinical problem. Rather it is the region of hyperglycemia and glycosuria *short of* acidosis that is of importance. The advocates of strict chemical control would try to minimize hyperglycemia and glycosuria, always mindful of course of the necessity of not overstepping into the highly undesirable region of hypoglycemic episodes. Those who oppose strict chemical control have been unconvinced that hyperglycemia and glycosuria, without acidosis, are of much consequence and have, therefore, not been concerned about patients spending most of their time with moderate hyperglycemia and some glycosuria.

Strisower and co-workers[78] have recently presented direct evidence concerning the relationship of chemical control with serum lipoprotein levels and Atherogenic Index values, *in this region short* of acidosis. These studies were performed in a

group of 17 institutionalized diabetic, schizophrenic women on the medical service of a large state hospital. The patients were all ambulatory. Since careful observation was possible for the group, it was deemed feasible to raise or lower insulin dosage in such patients for periods of many weeks or months so as to achieve an alteration in mean fasting blood sugar levels. During such periods of "control" (high insulin dosage) and "decontrol," but without acidosis (low insulin dosage), serial lipoprotein analyses were made. There is no doubt that alteration in insulin dosage provoked alterations in chemical control, for the chronic fasting blood sugar levels in essentially all patients were markedly lowered during high insulin dosage and raised during low insulin dosage The overall findings of the Strisower study are presented in Table XLV. There is a highly significant, appreciable average lowering of the Atherogenic Index associated

TABLE XLV

ALTERATIONS IN SERUM LIPOPROTEINS AND ATHEROGENIC INDEX VALUES IN RELATION TO CHEMICAL CONTROL OF DIABETES (17 PATIENTS)

Variable	*Mean Level** in "Control" Phase	*Mean Level*** in "Decontrol" Phase	*Difference* "Decontrol-Control"
S_f 0-12 Lipoproteins (mg/100ml)	385	415	+ 30 ($p < 0.001$)
S_f 12-20 Lipoproteins (mg/100ml)	73	71	− 2 (Not significant)
S_f 20-100 Lipoproteins (mg/100ml)	93	101	+ 8 ($p < 0.10$)
S_f 100-400 Lipoproteins (mg/100ml)	23	32	+ 9 ($p < 0.02$)
Atherogenic Index (units)	72	79	+ 7 ($p < 0.01$)
Mean Fasting Blood Sugar (mg/100ml)	105	191	+ 86 ($p < 0.001$)
Mean Insulin Dosage (units)	49	13	− 36

* Mean values of 150 blood samples representing a total study period of 220 pati[illegible] weeks

** Mean [illegible]

[illegible] ... are not complicating factors in

with the lower blood sugars of the "control" (high insulin dosage) phase contrasted with the other phase. These workers showed further that middle-aged patients showed a larger effect than did very elderly diabetic patients. Such data provide sound, biochemical support for the concept that strict chemical control of diabetes is of value in reducing one major factor associated with increasing the risk of premature coronary heart disease. It is hardly necessary to emphasize that this is *not* advocacy of insulin dosages sufficiently high as to provoke frequent episodes of hypoglycemia.

PROGNOSIS FOR THE DIABETIC PATIENT

It is regrettable that the scientifically unsupported notion that *diabetes per se* implies a high risk of premature coronary heart disease should have gained wide credence. The medical literature is replete with statements to the effect that, although diabetics need no longer die of acidosis or coma, they still are doomed to a complication of premature arteriosclerosis The *evidence* is quite otherwise. In the discussion above it was shown in quantitative terms that the major share (if not all) of the excessive risk of a complication such as coronary heart disease arises from Atherogenic Index elevation or diastolic blood pressure, or both. But this is an *average* finding for diabetic patients A particular diabetic patient can have escaped both the lipoprotein-Atherogenic Index elevation and the blood pressure elevation. For this patient there is no reason for the physician to be gloomy with respect to the prognostic outlook nor to generalize the increased risk of diabetes to this patient. If such a diabetic patient can maintain low or moderate Atherogenic Index and diastolic blood pressure values, *his* risk of premature coronary heart disease may be expected to be many times lower than the risk for many persons who are not diabetic. The point is that the physician has available to him valid, measurable criteria that determine, at a minimum, the largest share of the risk of vascular complications, namely the lipoprotein and blood pressure measurements Wide use of such criteria instead of the much less correct generalizations concerning diabetes will provide

exceedingly welcome relief to large number of diabetic patients who fear heart disease as an inevitable result of their being diabetic Furthermore, utilization of these valid criteria of coronary heart disease risk can prove to be invaluable aids to the physician in management of the diabetic, both in the areas of the planning of a regimen and in procurement of the patients' maximum cooperation in the control of his disease.

Chapter XIII

THE THYROID AND CORONARY HEART DISEASE

INTEREST has for decades centered about the question of the inter-relationships of thyroid function, blood lipid levels, coronary arteriosclerosis, and coronary heart disease. The clinical literature on this subject is a maze of confusion, contradictory statements, and sweeping opinions based upon scanty evidence and, in many cases, no evidence whatever. But few problems are of greater importance to the physician interested in coronary heart disease than to know the true status of the role of the thyroid and of thyroid hormone and its congeners. There are *several cogent reasons why this is true, among which are;*

(1) Hypothyroidism, spontaneous or iatrogenically induced elevates blood lipoprotein levels (especially S_f0-12 and S_f12-20), and hence elevates the Atherogenic Index

(2) Desiccated thyroid substance[79], thyroxine[80], and tri-iodothyronine[81] have all been demonstrated to be potent for *lowering blood lipoprotein levels and Atherogenic Index* values, not only in hypothyroid persons *but also* in euthyroid persons.

(3) The classical mode of production of arteriosclerosis in animals, ordinarily resistant, involves the use of thyroid ablation, either surgically, by radiation, or by thiouracil or related drugs

(4) A vast clinical literature indicates that hypothyroidism accelerates development of coronary arteriosclerosis.

BASIC CONSIDERATIONS

The chief interest in this text is in the field of subclinical coronary heart disease, that is the period when accumulation of

risk of future clinical coronary heart disease goes on silently, undoubtedly via the mechanism of progressive narrowing of the coronary arteries. It is, therefore, important to avoid confusing this phase of coronary heart disease with *extremis* phases of clinical coronary heart disease, such as angina decubitus. Thus preventive or therapeutic considerations that may apply to the person in the subclinical phase of coronary heart disease, either before the first clinical episode or during the interim period between clinical episodes, may not apply to the patient with severe angina pectoris or cardiac decompensation. This differentiation is commonly missed in much of the medical literature on the subject of thyroid and coronary heart disease. Let us suppose it has been demonstrated that administration of desiccated thyroid substance may intensify angina pectoris in some patients who already have angina pectoris. This *need not necessarily* have any bearing whatever upon the question of utilization of desiccated thyroid substance (and related agents) for purposes of achieving and maintaining lowered lipoprotein levels and Atherogenic Index values in persons free of clinical manifestations of coronary heart disease.

THE BLOOD LIPOPROTEINS AND ATHEROGENIC INDEX IN SPONTANEOUS MYXEDEMA AND INDUCED HYPOTHYROIDISM

The extremely high incidence of elevation in the blood cholesterol level *both* in spontaneous myxedema and in induced hypothyroidism have long been known to physicians. In recent years, with the availability of modern physico-chemical techniques it has been possible to identify the intimate nature of the blood lipid disturbance both in spontaneous and in induced hypothyroidism and myxedema. The lipoprotein findings for untreated spontaneous myxedema are illustrated below for two typical cases.

	S_f 0-12 (mg/100ml)	S_f 12-20 (mg/100ml)	S_f 20-100 (mg/100ml)	S_f 100-400 (mg/100ml)	Atherogenic Index (Units)
Case 1 44 year old woman	730	130	112	18	119
Case 2 60 year old woman	827	193	103	16	157

The major features of importance are the massive elevation in the S_f0-12 and S_f12-20 lipoproteins, the absence of any appreciable elevation in S_f20-100 and S_f100-400 lipoproteins, and the marked elevation of Atherogenic Index which results from the S_f0-12 and S_f12-20 lipoprotein elevation. The induction of hypothyroidism and myxedema by surgical means, by radioiodine, or by pharmaceutical agents of the thiouracil type produces a hypercholesterolemia of the same form, namely an elevation of S_f0-12 and S_f12-20 lipoprotein levels above the corresponding pre-treatment levels. Therapy of myxedema with desiccated thyroid substance, thyroxine, or tri-iodothyronine results in a reduction in level of the S_f0-12 and S_f12-20 lipoproteins.

The marked elevation of S_f0-12 and S_f12-20 lipoprotein levels and hence, the Atherogenic Index, in either spontaneous or induced myxedema would be expected to lead to an accelerated rate of development of subclinical coronary heart disease and, therefore, to a high risk of future clinical manifestations There exists no reason, on a priori grounds, to assume that Atherogenic Index elevation resulting from myxedema should behave any differently with respect to increasing coronary heart disease risk than would elevation for any other reason. Physicochemically and chemically the lipoproteins of the S_f0-12 and S_f12-20 classes, which become elevated in myxedema, are similar to those which occur in health and in a variety of other diseases. There is no reason why the risk tables of Chapter V should not be used in the case where lipoprotein elevation is produced by myxedema Yet there is current, in some quarters, the idea that the elevation in blood lipoproteins (or blood cholesterol) in hypothyroidism or myxedema is "safe," in that it neither accelerates coronary arteriosclerosis development nor increases the risk of clinical coronary heart disease. This idea is based upon inadequate evidence plus erroneous interpretation and analysis of what evidence does exist Blumgart and his co-workers[83] have sponsored the view that the blood lipid elevation in hypothyrodism and myxedema does not accelerate coronary arteriosclerosis Their evidence for this view deserves careful appraisal These workers have had experience with the therapeutic use of induced hypothyroidism for alleviation of intractable angina pectoris and

congestive heart failure. In a publication[53] dealing with eight patients who had survived one to thirteen years after surgical total thyroidectomy, Blumgart and co-workers drew the conclusion that "The results demonstrate that progressive atherosclerosis of the coronary arteries is not a necessary concomitant of increased blood cholesterol levels in hypothyroidism or of the hypothyroid state" This sweeping generalization would be important indeed if the evidence presented by Blumgart and associates could support it, but the evidence does not do so. The series of patients they reported included five men and three women.

For the five men, the following values are obtained from analysis of the data presented:

Mean age at thyroidectomy	31 0 years
Mean initial blood cholesterol level	197.0 mg/100ml
Mean duration of life in the myxedematous state	8.3 years
Mean blood cholesterol during the period of life in the myxedematous state	335 2 mg/100ml

For the three women, the following values are obtained.

Mean age at thyroidectomy	40.3 years
Mean initial blood cholesterol level	198 0 mg/100ml
Mean duration of life in the myxedematous state	6 2 years
Mean blood cholesterol level during the period of life in the myxedematous state	277.3 mg/100ml

Based upon gross, semi-quantitative evaluation of the postmortem state of the coronary arteries, the conclusion was drawn that the degree of involvement of the coronary arteries was certainly no greater and probably less than that generally witnessed in similar euthyroid individuals with the same disease process." No evidence was presented for such similar euthyroid individuals to facilitate this comparison Among many questions that must be asked is, "Are these eight patients representative, in their initial state before myxedema induction, of euthyroid individuals?" The mean blood cholesterol initially for the five men was 197 0mg/100 ml From data in the literature[54] the mean cholesterol level (by similar methods) for men of this age in the population at-large is 218.0 mg/100 ml The mean blood cho-

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matous average men would have accumulated by the age of 42.3 years, which is the age at which Blumgart's male patients died. As a result of the myxedema induction and the elevation of Atherogenic Index of 45 units resulting therefrom, those patients would have accumulated 45x8 3, or 374 units more than the average non-myxedematous man. Blumgart's males, therefore, at death would have accumulated a total of 2814 units (obtained by adding 374 to 2440) in comparison with 2440 units for non-myxedematous men at this age. Similar calculations are readily made for the women. The average non-myxedematous woman at 40 3 years has an Atherogenic Index of 55.5 units and by 46 5 years, an Atherogenic Index of 59.5 units. At 40 3 years, such a woman would have accumulated 1790 units. During the 6.2 years thereafter (corresponding to the myxedema period for Blumgart's female patients), average non-myxedematous women would accumulate (6 2) (57 5), or 357 additional units, giving a total accumulation of 1790 + 357, or 2147 units As a result of the myxedematous state, Blumgart's three women would have accumulated an extra 25x6 2, or 155 units Therefore, at 46 5 years, which is the age of death of Blumgart's women, they would have accumulated 2302 units in comparison with 2147 units expected for non-myxedematous women of the same age.

Elsewhere[23] it has been shown that the total accumulation (measured by Atherogenic Index multiplied by time) parallels extremely closely the quantitative changes in degree of coronary arteriosclerosis with age in the United States, wholly independent of any consideration of cause and effect relationships Therefore Blumgart could have expected his myxedematous men to have a 15 3% increase in degree of coronary arteriosclerosis compared with non-myxedematous men of the same age corresponding to the 15 3% greater accumulation calculated above. Similarly he could have expected a 7.2% increase in degree of coronary arteriosclerosis compared with non-myxedematous women of the same age, corresponding to the calculated 7.2% increase in accumulation due to the myxedema From the known extent of variation in degree of coronary arteriosclerosis in men of a particular age, or in women of a particular age, it can be estimated that to prove a 15.3% increase in degree of coro-

lesterol level initially for the three women was 198.0 mg/100 ml. For women of this age in the population-at-large the mean cholesterol level is 210 mg/100 ml. If blood cholesterol level is related to coronary arteriosclerosis development, it can be stated that the eight patients, *without* myxedema, should have showed an average, or slightly lower-than-average degree of coronary arteriosclerosis. The crucial issue at hand is how much would the period of life these patients experienced with some elevation of blood cholesterol have increased the expected degree of coronary arteriosclerosis above average?

This question can be answered utilizing the concept of accumulation of coronary arteriosclerosis. First, since the blood cholesterol elevation in myxedema is almost wholly in S_f0-12 and S_f12-20 lipoproteins, the extent of elevation of these lipoprotein classes can be calculated, since they are known from chemical data to contain 34% cholesterol by weight. Thus, for the five men in the series the mean elevation of blood cholesterol of 138.2 mg/100 ml above the initial value corresponds to an elevation of S_f0-20 lipoproteins of 138 2 over 0.34 or 407 mg/100ml. For the three women in the series the mean elevation of blood cholesterol of 79.3 mg/100 ml above the initial value corresponds to an elevation of S_f0-20 lipoproteins of 79.3 over 0.34 = 233 mg/100 ml. Since these lipoproteins inculde the S_f12-20, which receives a weighting of 1.75 times that of the S_f0-12 lipoproteins, the elevation in lipoproteins for the men corresponds to approximately a 45 unit increase in Atherogenic Index for the men and to a 25 unit increase in Atherogenic Index for the women. On the accumulative basis, where Atherogenic Index multiplied by time is considered (see Chapter VII), the average 34 year old man, whose Atherogenic Index is 68.6 units, will have accumulated 1834 units In the 8 3 year period (the length of time Blumgart's male patients were myxedematous; this average man would accumulate additional units Since by 42 3 years his Atherogenic Index, without myxedema induction, would be 77.3 units, the average Atherogenic Index for the 8.3 year period would have been 68.6 + 77.3 over 2, or 73.0 units. Therefore, the additional accumulation would have been 73.0x8.3, or 606 units. Adding 606 to 1834 gives 2440 units which non-myxede-

to the pre-therapy levels in spite of maintained administration of three grains of thyroid substance per day. This apparent "escape" phenomenon has a reasonable explanation. During the early period of administration of thyroid substance the patient has available the exogenously administered plus the endogenously produced thyroid hormone. As administration of exogenous hormone continues, endogenous thyroid hormone production is suppressed via the thyroid-thyrotropin system, until finally a point is reached where the *total* supply of thyroid available to the patient is not appreciably different from that available before the inception of administration of thyroid substance, except that it is by such a time largely exogenous rather than endogenous in source. A reasonable corollary of this explanation would be that in order to achieve maintained lipoprotein lowering by exogenous thyroid administration sufficient thyroid must be given so that even if complete shutdown of endogenous production of thyroid hormone occurs, there would still be more thyroid available to the patient than was available before the administration of the exogenous supply. From the long-term studies of Strisower and co-workers[85] it appears that with doses of 4 or 5 grains of U.S.P. desiccated thyroid substance per day such a point is reached for most persons within the usual ranges of lipoprotein distribution. With these doses the level of lipoproteins is lowered and is maintained lower without any evidence of an "escape" phenomenon. The magnitude of lowering of lipoprotein levels that were achieved with doses of 5 grains of desiccated thyroid substance per day is shown in the data of Table XLVI. There the 39 cases studied extensively by Strisower have been segregated into three separate groups, ranked according to initial level of the various lipoprotein classes. Thus not only is the effect of thyroid substance demonstrable, but its relationship with the initial lipoprotein status of the subject can be ascertained. Inspection of these data shows that with a dose of 5 grains of thyroid substance per day there occurs a sustained lowering in mean level of all four lipoprotein classes, S_f0-12, S_f12-20, S_f20-100, and S_f100-400 over the entire 36 week period of hormone administration. For any one of the four lipoprotein classes, the extent of reduction in lipoprotein level as a result of thyroid administration is greatest

nary arteriosclerosis among such male myxedema patients compared with non-myxedematous men would require careful quantitative assessment of degree of sclerosis in a series of about 100 myxedematous men and 100 non-myxedematous men of the same age. The demonstration of a 7.2% increase in coronary arteriosclerosis for the myxedematous women would require careful quantitative study of about 300 myxedematous women's coronary arteries and those of about 300 non-myxedematous women of the same age Yet by semi-quantitative grading Blumgart and his associates have made the decisions on five male patients and three female patients, respectively, without even presenting any data for matched non-myxedematous patients. The only conclusion reasonable in the light of these considerations is that the material studied by Blumgart and associates was entirely inadequate, and hence unsuitable, for attempting any answer to the question of the relationship of myxedema, hypercholesterolemia, and arteriosclerosis Certainly, their evidence should in no way even suggest the idea that the blood lipoprotein and Atherogenic Index elevation in patients with myxedema are of different meaning for coronary disease than they are in any other persons.

THE EFFECT OF DESICCATED THYROID SUBSTANCE UPON SERUM LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES

Strisower and co-workers[79] have carried out extensive investigations of the effect of desiccated thyroid substance upon the various lipoprotein classes *Dosage* of thyroid substance is a highly critical factor in such studies, for depending upon dosage and time of blood sampling, *apparently* paradoxical results may be obtained. With a dose of one to two grains of desiccated thyroid substance daily in most euthyroid adults very little alteration in lipoprotein level is observed. With a dose of three grains per day from the start most euthyroid subjects experience an appreciable lowering of S_f0-12 and S_f12-20 lipoprotein levels during the first few weeks of administration of the thyroid Thereafter, there occurs, in most cases, a progressive rise in the levels of these lipoproteins completely, or almost completely, back

effect of administration of 5 grains per day of thyroid substance on the Atherogenic Index values for the 39 patients described above is presented in Table XLVII. The patients are ranked in that tabulation upon their initial, pre-thyroid Atherogenic Index values. It is evident that the group with very high Atherogenic Index values showed a very marked drop in Atherogenic Index value in response to continuous administration of desiccated thyroid substance. This is, of course, precisely the group that would clinically be considered to be in need of lowering of the Atherogenic Index value with respect to prophylaxis of future coronary heart disease.

In the discussion of familial factors in coronary heart disease (Chapter VI) the families characterized by massive elevation of S_f0-12 or S_f0-12 and S_f12-20 lipoprotein levels were described. These families show the same type of lipoprotein derangement which characterizes myxedema, although they show no clinical stigmata of myxedema. Such families, none-too-rare in the United States population, are known to have an inordinately high risk of clinical coronary heart disease for those members of the family who *do* inherit the lipoprotein abnormality. Both from the biochemical viewpoint and for possible practical prophylactic reasons the response of persons characterized by this particular

TABLE XLVII

EFFECT OF FIVE GRAINS OF DESICCATED THYROID SUBSTANCE PER DAY UPON ATHEROGENIC INDEX VALUES IN RELATION TO PRE-THERAPY ATHEROGENIC INDEX VALUES

Mean Initial Atherogenic Index (units)	*Mean Atherogenic Index After 36 weeks on 5 Grains of Desiccated Thyroid Daily (units)*	*Change in Mean Atherogenic Index (units)*
Overall Group of 39 Cases		
70.0	52.0	− 18.0
The 10 Cases with highest Initial A.I. Values		
94.1	64.0	− 30.1
The 19 Cases with intermediate A.I. Values		
71.5	53.1	− 18.4
The 10 Cases with lowest Initial A.I. Values		
45.0	37.1	− 5.9

TABLE XLVI

BLOOD LIPOPROTEIN RESPONSE TO DAILY ADMINISTRATION OF FIVE GRAINS OF DESICCATED U.S.P. THYROID SUBSTANCE IN RELATION TO PRE-THERAPY LIPOPROTEIN LEVELS

Range of Levels (mg/100ml)	*Mean Initial Lipoprotein Level*	*Number of Subjects*	*Lipoprotein Level after 36 weeks on 5 grains of thyroid daily (mg/100ml)*	*Change in Mean Lipoprotein Level (mg/100ml)*
S_f0-12 Lipoproteins				
Over 400	127	16	340	− 87
300-400	350	15	295	− 55
Below 300	218	8	184	− 34
S_f12-20 Lipoproteins				
Over 100	145	8	47	− 98
50-100	76	17	29	− 47
Below 50	37	14	23	− 14
S_f20-100 Lipoproteins				
Over 100	120	13	94	− 26
70-100	81	10	73	− 8
Below 70	54	16	54	0
S_f100-400 Lipoproteins				
Over 50	88	10	45	− 43
25-50	36	10	21	− 15
Below 25	16	19	13	− 3

in those individuals initially characterized by the highest levels of that particular lipoprotein class, is somewhat less for the initially intermediate group, and is least for the group with the lowest lipoprotein levels. One possible interpretation of these findings is that individuals with the highest lipoprotein levels may be *relatively* deficient in thyroid hormone availability, even though on usual clinical grounds no evidence of frank hypothyroidism is present.

PRACTICAL CLINICAL IMPLICATIONS OF THE EFFECT OF EXOGENOUS THYROID SUBSTANCE UPON SERUM LIPOPROTEIN LEVELS

With respect to the potential application of the profound effect of desiccated thyroid subtance upon blood lipoproteins, it is of great interest to know how the overall Atherogenic Index value is affected by the administration of thyroid substance. The

TABLE XLVIII

RESPONSE OF PATIENTS WITH S_f0 20 HYPERLIPOPROTEINEMIA TO DESICCATED THYROID SUBSTANCE

Case No.	Age & Sex	Initial Lipoprotein Levels S_f0 12	S_f12 20	S_f20 100	S_f100 400	Atherogenic Index	Maximum Thyroid Dosage Reached and Duration of this Dosage*	Initial Body Weight (pounds)	Weight at time last sampling (on maximum thyroid dosage) (pounds)	Lipoprotein Levels at Time of Maximum Thyroid Dosage S_f0 12	S_f12 20	S_f20 100	S_f100 400	Atherogenic Index	Total Duration of Thyroid Administration including period on maximum dosage**
1	48M	554	136	212	86	137	3 grs for 5 mo	195	108	180	122	170	56	109	9 months
2	22F	658	139	28	0	95	5 grs for 7 mo	105	111	571	10	14	1	73	19 months
3	5M	643	51	43	2	81	6 grs for 4 mo	10	41	155	32	31	6	58	12 months
4	30F	665	98	13	2	92	5 grs for 2 mo	155	138	518	59	62	15	79	12 months
5	40F	533	61	16	8	75	5 grs for 2 mo	156	152	362	36	57	19	56	11 months
6	11F	822	131	66	0	117	5 grs for 4 mo	71	88	161	76	93	31	81	21 months
7	35F	938	118	83	6	130	7 grs for 1 mo	115	114	629	66	82	35	95	21 months
8	8F	617	99	31	8	86	5 grs for 5 mo	81	86	995	41	31	9	55	11 months
9	40M	920	201	110	10	148	7 grs for 2 mo	180	155	669	135	138	50	123	11 months
10	11F	935	155	98	2	158	8 grs for 4 mo	134	147	588	98	112	23	100	11 months
11	5F	815	110	57	10	115	3 grs for 15 mo	51	59	508	15	22	6	63	21 months
12	19M	1075	167	133	20	161	4 grs for 3 mo	170	168	905	108	172	31	145	9 months
13	58F	888	175	218	79	177	1 grs for 2 mo	151	151	591	112	151	50	119	7 months
14	37M	826	117	151	76	145	2 grs for 2 mo	156	159	636	112	291	214	168	6 months
15	68F	1055	160	161	31	165	4 grs for 2 mo	166	164	701	135	129	50	125	7 months
16	19M	580	171	116	28	115	3 grs for 1 mo	189	177	431	103	127	30	89	13 months

* These studies are still in progress. The "maximum" thyroid dosage is simply that which has been reached at the time of this evaluation, and in no way implies maximum thyroid tolerance of the patient.

** In general the patients were started with a dosage of 1 grain of desiccated thyroid per day and the dose built up over varying periods thereafter, depending upon response.

familial hyperlipoproteinemia is of intense interest. Sixteen such subjects have been treated with desiccated thyroid substance for varying periods of time. The results achieved are presented in Table XLVIII. It is evident that such persons are distinctly capable of responding to administration of thyroid substance with a marked lowering in the level of S_f0-12 and S_f12-20 lipoprotein. Furthermore, many such responses occur without weight loss or even in the face of a net gain in weight. Clinical evidence of thyroid toxicity has been a rare occurrence in these subjects

The clinician reflecting upon these large effects of exogenous thyroid substance on serum lipoprotein levels and Atherogenic Index values will, in many instances, still be hesitant to consider the use of exogenous thyroid substance as a preventive measure in the sub-clinical phase of coronary heart disease. He will undoubtedly be mindful of the fact that caution is indicated in the rate of buildup of the dosage of thyroid substance in patients with myxedema, where too energetic thyroid replacement therapy has been reported to result in myocardial infarction The presumed mechanism in such cases is an increased caloric expenditure by the myocardium in the presence of an embarrassed coronary blood flow resulting from extensive coronary arteriosclerosis The clinician will also be mindful of the reports that angina pectoris can be exacerbated by the administration of thyroid-active agents and that intractable angina pectoris can be relieved in some cases by thyroid ablation. But the patient with frank and long-standing myxedema and the patient with intractable angina pectoris are hardly those upon whom the broad interest in possible use of thyroid substance to diminish the rate of progression of sub-clinical coronary heart disease is focussed Rather the persons of interest are relatively youthful individuals with massive elevation in lipoprotein levels and Atherogenic Index values. The outlook for such persons is gloomy unless their lipoprotein status can be improved and maintained so for long periods of time. Some such subjects will show minor calorigenic effects of exogenous thyroid substance; others will not. Careful clinical observation of these persons during administration of thyroid substance is essential. Biochemistry, biophysics, and mathematics can aid

Chapter XIV

OCCUPATION, STRESS, PHYSICAL EXERCISE, AND CORONARY HEART DISEASE

It is not the need of a chapter in this book in which to place "residual" material that leads to the grouping of occupation, stress, and physical exercise together in the discussion of each in relationship with coronary heart disease. Rather, this grouping results from the observations (to be detailed below) showing that occupation is in some way related to coronary heart disease and from the emphasis placed by some investigators either upon stress or physical exercise as the factors accounting for the occupational differences in incidence rate of coronary heart disease Unfortunately, this area is considerably beclouded by semantic difficulties, by emotionalism, by pre-conceived concepts, and by inadequate quantitative data. Yet it is an important area, for every physician faces daily questions referable to this area from his patients with coronary heart disease and from those who would like to avoid that disease

Semantic and measurement difficulties surround one of these factors especially, namely stress Definitions of emotional, occupational and life stresses are nearly as frequent as are investigators of the problem Qualitative impressions are rife. Many are certain that the *pace of modern living* create stresses upon man never before equalled in history, although even semi-quantitative evidence to support this statement has not yet been forthcoming Such workers point to the apparently real rising incidence of clinical coronary heart disease in Western countries over the past several decades and to the pace of living in these regions over the same time period. Then they state flatly that it is obvious that the stress is clearly the basis for the increase in

clinical medicine, but they are hardly intended to be a replacement for seasoned clinical judgment. If calorigenic effects should develop and should be deemed clinically dangerous, then these particular persons probably cannot take advantage of the lipoprotein-lowering effect of thyroid substance. Most persons receiving thyroid substance will not show calorigenic effects sufficient to warrant discontinuation of thyroid administration.

There have recently been reported a few cases receiving tetraiodothyroacetic acid[86] where lowering of blood lipids was achieved without appreciable alteration of the basal metabolic rate or other evidence of calorigenic effects. This has raised hopes[87] that a pharmaceutical agent might be at hand which might provide the desirable effect upon blood lipoprotein levels while averting the unwanted possible calorigenic action. However, *these studies were not controlled by comparison* of the effects of desiccated thyroid substance on the same patients, a highly necessary control. Strisower and co-workers showed that many patients in their series exhibited no evidence of appreciable calorigenic action, such as weight loss, or such effects as pulse rate increase, but still showed marked lowering of lipoprotein levels. Nevertheless, inasmuch as the remarkable effect of thyroid-active substances upon blood lipoproteins has not been proved to be part of the calorigenic action of such agents, pharmacologic studies directed toward achievement of derivatives which may dissociate these effects appear worthwhile.

lying evidence may perhaps be somewhat stronger than critical evaluation would reveal it to be

OCCUPATION AND CORONARY HEART DISEASE

Consideration of this overall area may logically start with evaluations of occupation in relation to coronary heart disease, for occupational "stresses" have been indicted by many as a major predisposing factor in coronary heart disease. There do exist some factual data concerning the incidence rate of coronary heart disease in various occupational categories. Morris[88] has been especially active in the evaluation and presentation of data pertinent to occupational incidence rate of clinical coronary heart disease His studies indicating a higher frequency of clinical coronary heart disease and a more severe form of coronary heart disease in the drivers of double-decker London buses compared with the conductors of such buses are now classic in the medical literature. He has, further, provided data summarizing the incidence rate of clinical coronary heart disease in a wide variety of occupational categories for Great Britain. These occupational groups and their coronary heart disease incidence rates are listed in Table XLIX There is every reason to consider that occupational differences of appreciable magnitude do exist in the incidence rate of clinical coronary heart disease, well above any attributable to statistical sampling errors. It is, rather, the step beyond this conclusion which is so difficult. *Why do* occupational differences in incidence rate of clinical coronary heart disease exist? Morris recognized the difficulties involved in interpretation of the occupational differences in coronary heart disease and especially that no one ready explanation would be considered to explain all the observations Among the major possibilities that have received consideration are (1) The type of person who, in general, makes the choice of a particular occupation, or has it effectively made for him by circumstances, may differ in many ways from the type of person in some other occupation Physical habitus, muscularity, intellect, temperament, background and a host of other factors could well help determine who is to be found in a particular occupation. Should this be the major basis

incidence rate of clinical coronary heart disease. Yet no such conclusion seems obvious to the critical observer who places some reliance upon quantitative methods in modern medical science. It has been pointed out previously (Chapter XIII) that the quantitative disciplines do not in any way invalidate the continuing necessity for clinical judgment in medicine, but on the other hand this statement does not imply that unbridled impression can serve as evidence in lieu of quantitative measurement.

The essence of the difficulty with the evaluation of stress as a potential factor in coronary heart disease lies in the variability of its definition and the almost complete absence of satisfactory methods for its measurement, even on a crude, semi-quantitative basis. This necessarily makes any reasonable evaluation of its possible significance difficult, at a minimum. One finds it unsatisfactory to accept quantitation in terms of stressful situations, personal, social, economic, or other inasmuch as what really is of concern is the effect of any particular stressful situation upon a particular individual. A set of circumstances mildly stressful to one person can readily be conceived to be either mildly, moderately, or overwhelmingly stressful to some other person. Hence, what is needed is some method of quantitating the nature of the interaction of the situation with the individual and the extent of effect of such interaction upon that individual. Even if such a method were of semi-quantitative character, but objectively executed, involving a grading of stress on a scale of plus one to plus four, enormous progress could then be made in the evaluation of any possible relationship of stress in humans with the evolution of coronary heart disease. But no such method has been described, and worse yet, most evaluations to date have involved *retrospective* evaluation of the stress, once the biochemical or clinical alterations of interest had already been observed, a procedure fraught with massive danger of bias. Nevertheless, it is of some merit to examine what evidence has been brought forward purporting to relate stress to coronary heart disease in man. Especially is this important to do since some of the advocates of the stress concept are rather positive in their assertions, leaving the impression that the under-

require identification and a determination of whether or not *new*, or *independent*, information is provided with respect to coronary heart disease. This point deserves amplification. Suppose that the circumstances of a particular occupation were such as to modify significantly the dietary habits of persons in that occupation, either as a result of location, availability of certain foods, or social circumstances within the occupation. It would be possible that animal sources of fat, for example, might be increased in the habitual diet. From previous considerations (Chapter X) it would be predicted that this dietary alteration would provoke an elevation of the S_f0-12 and S_f12-20 lipoproteins, and through this, the Atherogenic Index would be elevated, and would hence lead to an increase in expected incidence rate of coronary heart disease for the occupational category itself. But this would really not be new, or independent information concerning factors involved in the evolution of coronary heart disease, for it would have reduced itself to one of the two known basic factors, namely blood lipoproteins and blood pressure level. To be sure it would be important to identify the fact of a habitual alteration in diet being a basis for an occupational predisposition to coronary disease, but this would be a discovery of minor magnitude in comparison with adding an additional basic factor to the two which are known.

(2) The many and varied stressful features of certain occupations have been considered by Morris and others as a possible basis for observed differences in coronary disease incidence rates. Morris concluded that, considering all the occupational groups involved, it would be difficult to frame a hypothesis built around stress of the occupation that would be satisfactory to explain the findings Others have quickly pointed to the differences between the stressful factors in the occupational life of a bus driver in congested London traffic in comparison with the presumed lesser stresses in that of the conductor of the double-decker bus. Whether the bus driving in congested traffic is stressful or relaxing to a London bus driver is not as simply decided as some would make it seem. Much depends upon the reaction of the type of man who is a bus driver in the evaluation of what stress he experiences in his occupation Even if it were conceded that bus

TABLE XLIX

DEATH RATE FROM CORONARY HEART DISEASE IN RELATION TO OCCUPATION
(45-64 YEAR OLD MEN
ENGLAND, AFTER MORRIS)

Occupational Category	*Death Rate from Coronary Heart Disease (number per million per year)*
Hairdressers, etc.	880
Makers of Textile Goods	770
Typists and other Clerks (Non-Civil Service)	730
Fitters, Mechanics, Tool Makers, etc.	560
Messengers and Porters, etc.	500
Railway Engine Drivers	*480*
Postmen and Sorters	460
Boot and Shoe Makers, Repairers	450
Smiths and Skilled Forge Makers	420
Metal Machinists	380
Coal Hewers and Getters	290
Water Transport Dock Laborers	270
Coal Mine Workers below ground, except Hewers and Getters	230
Other Workers in Building, etc.	170
Agricultural Gardeners, Laborers, etc.	150

for the differences in occupational incidence of coronary heart disease, the problem would reduce itself to that of understanding what features of particular types of persons account for an inordinate susceptibility to coronary heart disease. Illustratively, if obese men should represent a much higher proportion of those engaged in one occupation versus others, that occupation would be expected to show a higher incidence rate of coronary heart disease than the others because obesity is definitely known to increase the risk of such disease (See Chapter IX) This would be true even if no features of the occupation or the interaction of the individual with his occupational environment existed. On the other hand it could be that persons of a particular type might tend to select a certain occupation, and that the interaction of the occupational environment with that particular type of individual might lay the groundwork for future manifest coronary heart disease. In such an event that interaction would

and blood pressure, or whether it provides a third factor of *independent* importance in coronary heart disease. Occupational studies, including the physical activity factor, are unquestionably needed to provide some of the critical answers.

RELATIONSHIP OF OCCUPATION WITH FACTORS KNOWN TO BE OF IMPORTANCE IN CORONARY HEART DISEASE

(a) Blood Lipoproteins, Atherogenic Index and Occupation

Several years ago the author and his colleagues undertook some long-range studies of the various characteristics of the human population which influence habitual distribution of blood lipoproteins. With the already-available knowledge that even for a specific age and sex group, considerable variability still characterizes the population with respect to blood level of such lipoproteins as the S_f0-12, S_f12-20, S_f20-100, and S_f100-400 classes, it seemed extremely worthwhile to make a continuing effort to ferret out possible bases for such variability. Further, serial study of population groups allows for the possibility of understanding some of the sources of variability of lipoprotein level within individual subjects. Occupational category was considered as one major variable of importance for study. Since it was desirable to eliminate certain types of extraneous sources of possible variation, the decision was made to study subjects in one industry, working and residing in one general locale. In this way, such possible sources of variation as climatic, geographic, and general features of the occupational environment are greatly minimized. Of course, the persons who work in one industry do have a previous background of differing geographic contacts, of having been in other industrial locations, and other features that render them heterogeneous. Nevertheless the common environment they share at the time of study which for most of them was over one year after they had been employed in this single industrial area would have tended to decrease heterogeneity in as practical a way as is possible for such studies. In this industry* a reasonable distribu-

*University of California Radiation Laboratory at Livermore, California (Employees number approximately 2500)

driving were more stressful than conducting, there remain numerous other pairs of occupations, differing in coronary disease incidence rates, where such possible stress differences are not so apparent. For example, clerks in England have a higher coronary heart disease rate than postmen. Assessment of stress factors for these two groups is not immediately obvious. Unfortunately many who have assigned stress ratings to occupational groups have done so *retrospectively*, once it was known which occupational group had the higher incidence rate of coronary heart disease. It is regrettable that no more objective and quantitative approach to stress evaluation is available to replace the highly subjective, retrospective one.

(3) *Physical Activity in Occupations:* Morris felt that his own evidence as a whole pointed most strongly to physical activity of the occupation as the feature of prime importance in determination of the incidence of coronary heart disease for the occupation. Thus the bus drivers in London double deckers, *seated* in their occupational activity for some eight hours of every working day, do have far less activity *at work* than the conductors, who make numerous trips up and down the bus stairs daily. Upon review of the other occupational categories, Morris found a reasonable inverse relationship between the physical activity of the occupation and the incidence rate of clinical coronary heart disease. This inverse relationship appears, from Morris' data to be well-established. The important question which follows is "How does it operate?" Does physical activity at work of and by itself really provide some degree of protection against coronary heart disease? *If it does, would advocacy of physical exercise for those* in more sedentary occupations be indicated in the effort to minimize their risk of coronary heart disease? These are points of enormous practical clinical consequence. Clearly it would be essential to learn whether the physical activity *per se* of certain occupations is the essential feature, or whether this is a reflection of some other feature, known or unknown. If physical activity *is* important, it must operate by some definable mechanism. In approaching this issue of mechanism, it would be important to determine whether physical exercise (if it be a factor) in any way influences the two major known factors, blood lipoproteins

and blood pressure, or whether it provides a third factor of *independent* importance in coronary heart disease. Occupational studies, including the physical activity factor, are unquestionably needed to provide some of the critical answers.

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*University of California Radiation Laboratory at Livermore, California. (Employees number approximately 2500)

tion of occupations is represented, including unskilled labor, highly skilled labor, clerical, professional, scientific, and executive groups.

In all twenty-nine occupational listings, obtained from the personnel department records, characterized the individuals from this population sample under study. All subjects had periodic complete medical examinations at intervals of eighteen months, at which time the lipoprotein analyses were made. It is understood that at times a particular personnel listing, e.g., engineer, can mean work loads differing appreciably within the category from individual to individual. Thus the physical activity at work for each engineer can hardly be expected to be identical, but it was not deemed feasible to sub-categorize so extensively as to arrive at a great multplicity of sub-groups each containing so few individuals as to make analysis of the findings impossible. Therefore each of the twenty-nine occupational groups was kept together as a single entity. The age for each group was not identical, ranging plus or minus approximately five years on either side of 35.0 years of age. For comparison of lipoprotein levels in one occupational category with another, the small correction of the lipoprotein level for each category to what it would be at 35.0 years was made. Such small corrections are extremely good, since the age trend for each lipoprotein class is very well established (Table XXIV). The data for all twenty-nine occupational categories are presented in Table L. The range of mean Atherogenic Index values for the various occupational categories is truly startling. Excluding some of the categories where limited numbers of subjects were available for study, some of the differences observed are obviously real and of major magnitude For example, the series of fifty custodians show the low mean Atherogenic Index of 60.6 units which may be compared with the overall group of *all* occupations for which the mean Atherogenic Index is 69.1 units. The difference of 8.5 Atherogenic Index units is so large that sampling errors alone would lead to this large a difference about once in one hundred times. (See Table L for method of proving this In this case SE = 3 5, $t = 2.4$) Similarly, comparison of one of the categories showing a very high value, e.g., tool and die makers with a mean Atherogenic Index

TABLE L

Atherogenic Index Values in Twenty Nine Occupational Categories in One Industry (Male Subjects)

(Ranked from Highest Atherogenic Index Values to Lowest)*

Occupational Category	*Number of Men*	*Mean Age (years)*	*Atherogenic Index (adjusted to 35 0 years) (units)*
Computer and Duplicating Machine Operators	21	31 1	79 6
Truck and Bus Drivers	24	33.6	79 4
Buyers	11	39 0	77 8
Tool and Die Makers	62	36 0	77 7
Mathematicians	61	28.3	75 9
Laboratory Technicians	47	31.5	73 8
Journeyman Machinists	77	36 9	73.6
Firemen	19	36.5	72.3
Painters	17	41.2	72.2
Mechanical Technicians	90	34 8	71 7
Carpenters	21	35.4	71 4
Welders	14	39 4	70.6
Riggers and Equipment Movers	10	36.3	69 7
Electricians	45	36 7	69 7
Engineers	276	35 4	69 6
Physicists	227	30 6	69 4
Draftsmen	110	33 1	69 2
Executives (Assistant and Junior Classifications)	68	36 5	68 6
Steam Fitters and Boiler Operators	21	45.2	68.3
Clerks	23	32 3	67.8
Electronic Technicians	170	32.6	67 8
Chemists	77	31.2	67.6
Machinists and Machinists Helpers	74	37 4	66 7
Police Officers	105	41 4	65 9
Accelerator Operators	70	31 4	63 1
Storekeepers	30	35.2	62.8
Laborers	40	39 9	61 4
Custodians	50	49 1	60 6
Sheet Metal Workers	22	43 2	55.2
Overall Group (All Occupations)	1885		69 1

* Standard Deviation of the Atherogenic Index for the overall group is approximately 25 units Therefore to test whether the mean for any occupational group is significantly different, the t test can be applied The standard error is SE = $\frac{25}{\quad}$,

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value of 77.7 units with a category with a *low mean Atherogenic* Index value, e.g. custodians with a mean Atherogenic Index value of 60.6 units reveals that there is less than one chance in 1000 *that so large a difference could arise by sampling alone. The con*clusion is safe that the difference observed is real.

It is of major consequence that real and *large* differences in mean Atherogenic Index values exist between men in various occupational categories. An estimate of the meaning of some of the differences observed is readily made by reference to Table XV. Thus, since differences such as those between values of 75 and 60 Athrogenic Index units have been shown to exist, incidence rates of coronary heart disease can be expected to differ by a factor of 4.97 over 2.59, or 1.9 *times* on the basis of the Atherogenic Index alone! Therefore, some insight is available as to part, at least, of the basis for occupational differences in incidence rate of coronary heart disease. What is of importance to determine is *why* some occupational categories should show different Atherogenic Index values from others Such features as the type of person who enters the occupation, the relative weights of the individuals, their smoking habits, and their dietary habits, deserve evaluation since such features have been shown to be of consequence with respect to Atherogenic Index values. The relative weights and the cigarette smoking habits for the men in the various occupational categories of Table L are available, since their weights were measured and they had been questioned concerning cigarette smoking during the examination. These data are presented in Table LI for each of the occupational categories Also in this table the combined mean value for all occupations characterized by Atherogenic Index values above the overall mean and the combined mean value for all occupations with Atherogenic Index values below the overall mean is presented Neither for relative weight nor for cigarette smoking can it be demonstrated that those occupations with high Atherogenic Index values are different from those occupations with low Atherogenic Index values Therefore it is clear that the broad features of the difference in Atherogenic Index with occupational categories cannot be explained either from differences in weight of the individuals or from differences in cigarette smoking habit

TABLE LI

RELATIVE WEIGHTS AND CIGARETTE SMOKING HABITS IN OCCUPATIONAL CATEGORIES RANKED UPON ATHEROGENIC INDEX

Occupational Category	*Number of Men*	*Mean Atherogenic Index (units)*	*Mean Relative Weight*	*Mean Number of Cigarettes Smoked Per Day*
Computer and Duplicating Machine Operators	21	79.6	1.08	10.7
Truck and Bus Drivers	24	79.4	1.06	8.7
Buyers	11	77.8	1.13	15.4
Tool and Die Makers	62	77.7	1.05	11.9
Mathematicians	61	73.9	0.99	8.0
Laboratory Technicians	47	73.8	1.02	11.4
Journeymen Machinists	77	73.6	1.05	9.2
Firemen	19	72.3	1.16	20.1
Painters	17	72.2	1.02	16.4
Mechanical Technicians	90	71.7	1.05	12.1
Carpenters	21	71.4	1.06	10.9
Welders	14	70.6	1.06	8.3
Riggers and Equipment Movers	10	69.7	1.07	10.5
Electricians	43	69.7	1.06	13.3
Engineers	276	69.6	1.05	8.9
Physicists	227	69.4	1.02	5.5
Draftsmen	110	69.2	1.02	9.4
Executives (Assistant and Junior Classifications)	68	68.6	1.05	15.9
Steamfitters and Boiler Operators	21	68.5	1.07	6.9
Clerks	23	67.8	1.00	13.4
Electronic Technicians	170	67.8	1.03	9.8
Chemists	77	67.6	1.05	7.1
Machinists	74	66.7	1.03	10.5
Police Officers	103	65.9	1.08	15.3
Accelerator Operators	70	63.1	1.01	8.9
Storekeepers	30	62.8	1.02	10.1
Laborers	40	61.4	1.07	12.0
Custodians	50	60.6	1.08	9.0
Sheet Metal Workers	22	55.2	1.04	12.7
All Occupations with Atherogenic Index Means Above 69.1 (the overall mean)	1133	71.4	1.041	9.4
All Occupations with Atherogenic Index Means Below 69.1 (the overall mean)	750	65.7	1.015	10.9

The failure of difference in body weight to explain the Atherogenic Index difference with occupation does not rule out the possibility that fatness may be important in this connection. The relative weight determination does not, of course, distin-

guish body weight made up of fat from that made of muscle, for example. It would still be possible that whereas the occupations characterized by low Atherogenic Index values do not show lower body weights, they might still represent individuals with less body fat and more muscle than the occupations with high Atherogenic Index values. This brings us to the question of the physical activity associated with various occupations. Four of the occupations with the lowest mean Atherogenic Index values, the laborers, the custodians, the accelerator operators and the storekeepers, are all characterized by extensive physical activity at work. *The four occupations with the highest mean Atherogenic* Index values, the computer and duplicating machine operators, *the truck and bus drivers, the buyers, and the tool and die makers* are certainly characterized by much less physical activity at work. It is not as readily apparent, however, that the occupations with an intermediate mean Atherogenic Index value are characterized by an intermediate degree of physical activity at work. However, other factors may in part operate here too. For example, the physicists do smoke significantly fewer cigarettes than the group as a whole, which will to some extent alter their position on the Atherogenic Index scale. Also, it must be remembered that, if physical activity *is* a major factor, possible differences in physical activity *outside* of work must also be considered Certain tests of the physical activity explanation do not, superficially at least, seem to provide consistency Thus physicists can be divided into two groups, the theoretical physicists and the experimentalists. It would be expected, on the average, that the experimental physicists have a greater degree of physical activity in their occupation than do the theorists. Yet the 45 theoretical physicists in the overall group of physicists showed an average Atherogenic Index of 65.1 units, whereas the 182 experimental physicists showed an average Atherogenic Index of 70 5 units. This is in the opposite direction from the expectations based upon physical activity of occupation alone as the basis for the observations

In the main, it does appear that the data concerning Atherogenic Index values for various occupations is consistent with the concept that physical activity at work is an important determinant, *but that in* selected groups other factors may operate to distort

this relationship. The findings are also, in the main, *consistent* with Morris' hypothesis that the physical activity of certain occupations is a protective factor against development of clinical coronary heart disease. The observations of a relationship between occupations and Atherogenic Index values need extensive broadening and understanding, for this area may provide a major clue to understanding one basis for the relationship of occupation with incidence rate of coronary heart disease.

TABLE LII

DIASTOLIC BLOOD PRESSURES IN TWENTY-NINE OCCUPATIONAL CATEGORIES IN ONE INDUSTRY

Occupational Category	*Number of Men*	*Mean Age (years)*	*Diastolic Blood Pressure in mm Hg (adjusted to 35.0 years)*
Painters	17	41.2	79.7
Firemen	19	36.5	73.6
Carpenters	21	35.4	73.1
Machinists and Machinists' Helpers	74	37.4	72.9
Clerks	23	32.3	72.9
Tool and Die Makers	62	36.0	72.1
Custodians	50	49.1	71.5
Draftsmen	110	33.1	71.4
Journeyman Machinists	77	36.9	71.4
Truck and Bus Drivers	24	33.6	71.4
Electronic Technicians	170	32.6	71.3
Mathematicians	61	28.3	71.3
Storekeepers	30	35.2	71.3
Computer and Duplicating Machine Operators	24	31.1	71.2
Chemists	77	31.2	71.0
Physicists	227	30.6	70.9
Steamfitters and Boiler Operators	21	43.2	70.9
Engineers	276	35.4	70.9
Mechanical Technicians	90	34.8	70.5
Accelerator Operators	70	34.4	70.4
Police Officers	105	41.4	70.3
Executives (Junior and Assistant Classifications)	68	36.3	70.2
Buyers	11	38.0	70.2
Electricians	43	36.7	69.8
Laboratory Technicians	47	31.5	69.5
Laborers	40	39.9	69.1
Sheet Metal Workers	22	43.2	68.5
Riggers and Equipment Movers	10	36.3	68.1
Welders	14	39.4	66.3

(b) Diastolic Blood Pressure and Occupation

The diastolic blood pressures were routinely measured for the same group of 1883 men whose Atherogenic Index values were determined. The mean diastolic blood pressures, adjusted for the small age differences to an age of 35.0 years, are presented in Table LII. The only outstandingly high occupational group on the diastolic blood pressure scale are the painters. Statistical test indicates that there is less than one chance in one hundred that the extent of elevation observed would arise by sampling alone No other single occupational category can be proved to show diastolic blood pressures higher than the group as a whole. On the low side no single occupational category can be proved to show diastolic blood pressures different from the group as a whole. In general the means of the diastolic blood pressure show less spread than the means of the Atherogenic Index values for the different occupational categories. It does not appear, therefore, that variation of blood pressure with occupational category can help appreciably to account for variation in incidence rate of coronary heart disease. However, the pressures recorded here are taken after reclining 10 minutes. It cannot be stated, therefore, that members of certain occupational categories do not show episodic diastolic blood pressure elevations of consequence, even though their sustained diastolic pressures are not unusual.

OCCUPATIONAL "STRESS" AND ATHEROGENIC INDEX VALUES

Several recent publications[89, 90, 91] have referred to effects of emotional and occupational stress upon blood lipid levels. The occupational categories described above have been subjected to preliminary analysis, difficult as evaluation is in this area, for effects of such factors as job responsibility and demands upon Atherogenic Index values. From all the occupational categories together, those individuals were selected out who are listed on personnel records as supervisors, foremen, and coordinators, all of which are positions of special responsibility The mean Atherogenic Index for the entire group of 62 such men was found to be

68.6 units, contrasted with 69.1 units for the overall group of 1883 men There is, therefore, no suggestion here that responsibility positions are characterized by any features that tend to elevate blood lipid values As another test of the effect of responsibility of position, the entire group of engineers (one of the largest single categories available for analysis) was divided into subgroups based upon their official professional ratings. Higher professional ratings are accompanied by increased responsibility, increased demands, and a higher income. After adjustment of the Atherogenic Index values to 35.0 years of age for all the professional rating groups (since the higher rating groups were slightly older than those of lower rating), no significant difference was found to exist between engineers with the lowest professional ratings, for those with intermediary ratings, or for those with the highest professional ratings If such factors as responsibility, demands, and frustration are really of consequence with respect to blood lipid levels, then it appears clear that currently reasonable approaches to measuring such stress features are inadequate to allow for discerning effects.

THE DIETARY BASIS FOR SO-CALLED OCCUPATIONAL "STRESS" EFFECTS

Friedman, Rosenman, and Carroll have recently reported[23] on changes in the serum cholesterol level purported to be the result of cyclic occupational stress in accountants, a stress they referred to as "socioeconomic stress" This stress was described by them as "a particular and rather specific type of emotional activity, namely that concerned with excessive "drive," competition, meeting "deadlines," and economic frustration" They were trying to study a form of stress further described by them as one which imposed a "sense of urgency" upon the subjects. It is of interest to note the basis upon which these authors selected this particular form of stress. Having convinced themselves that socioeconomic stress was correlated with the incidence of clinical coronary heart disease, they wanted to find out what kind of socioeconomic stress might be of importance. They therefore interviewed, by questionnaire, 162 executives of a large oil com-

pany, a railroad company, and 3 advertising agencies plus 47 physicians "actually treating cardiac patients." Since approximately 70% of both the lay and professional group chose the description of "socioeconomic stress" alluded to above, these investigators felt this must be the type worthy of study with respect to pathogenesis of clinical coronary heart disease. While this is a novel technique for deciding the probable etiology of disease, it is of interest to examine critically the far-reaching conclusions arrived at by these workers, for even accidental approaches to many problems have often led to highly important findings. Accountants were chosen as subjects because there existed, according to these investigators, a socioeconomic stress in these men predictably phasic enough during the first 5 months of the calendar year to allow periods of respite for control observation.

The *period from April 2 to April 15 was considered by* Friedman and co-workers to represent "severe stress," whereas May 14 to May 21 a period of "maximal respite" from stress In all, 39 accountants participated in the study throughout the entire period. From the data presented by these workers the following are the mean serum cholesterol levels for "Maximal occupational stress" and for "maximal respite";

During "Maximal Occupational Stress," Mean Cholesterol =	230 mg/100ml
During "Maximal Respite," Mean Cholesterol =	222 mg/100ml
Difference	8 mg/100ml

In order to evaluate whether or not dietary changes during these periods might have accounted for the serum cholesterol difference shown above, these workers took a very detailed dietary history for the two critical periods, April 2-9 ("maximal stress") and May 14-21 ("maximal respite"). Since so much reliance is placed upon these dietary records by the authors, our first approach must be to accept the dietary evaluations at face value and to determine whether they support the conclusion arrived at that stress itself, rather than dietary changes, was responsible for the observation of a change in mean cholesterol level of 8 mg/100ml The accountants were divided into two groups, depending upon the type of accounting they did Dietary evaluations were presented by Friedman and associates for

"maximal respite," and "maximal stress." The mean number of calories taken in daily for the combined group of 39 accountants during "maximal stress" was 1845 calories, whereas during "maximal respite" it was 1783 calories Therefore, at face value, the accountants ingested 63 fewer calories per day during "maximal respite" then they did during "maximal stress." This caloric difference the investigators stated could not possibly have accounted for the 8 mg/100ml change in serum cholesterol upon which their thesis rests. Is this true? Friedman and associates made no effort whatever to test whether this caloric change could or could not explain the 8 mg/100ml change in cholesterol level. Instead they simply stated that it could *not*. But there do exist ample dietary data to test this issue quantitatively.

In the discussion of overweight and alterations of overweight, a "natural" experiment was described in which 374 subjects were studied twice at approximately one and one half year intervals. Those who lost weight showed lowering of s_f0-12, s_f12-20, s_f20-100, and s_f100-400 lipoprotein levels, whereas those who gained weight, showed increases in the levels of all these lipoproteins. Those who did not change in weight did not change significantly in lipoproteins. Taking all those data together, we have the following straight-forward estimations,

For 1 pound of weight loss in a time interval *of* 62 4 weeks,
the mean fall in s_f0 12 lipoprotein level = 1.5 mg
the mean fall in s_f12 20 lipoprotein level = 0 4 mg
the mean fall in s_f20-100 lipoprotein level = 1 7 mg
the mean fall in s_f100-400 lipoprotein level = 2 1 mg

In that observation period, subjects were gaining or losing weight at various rates, some over the entire 62 4 week interval, others, undoubtedly, over a small fraction of that interval. Most of the subjects did not even know their weight was changing. The *average* rate of caloric restriction to lose one pound of weight in 62 4 weeks is estimated as follows. Allowing for some water in body fat, it requires a restriction of approximately 4000 calories to lose one pound of weight If this is to be lost, on the average, in 62 4 weeks, *the daily caloric* restriction must be 4000 over 62 4x7 or 9.2 calories per day. This number of calories restricted per day must, therefore, account for the falls in

pany, a railroad company, and 3 advertising agencies plus 47 physicians "actually treating cardiac patients." Since approximately 70% of both the lay and professional group chose the description of "socioeconomic stress" alluded to above, these investigators felt this must be the type worthy of study with respect to pathogenesis of clinical coronary heart disease. While this is a novel technique for deciding the probable etiology of disease, it is of interest to examine critically the far-reaching conclusions arrived at by these workers, for even accidental approaches to many problems have often led to highly important findings. Accountants were chosen as subjects because there existed, according to these investigators, a socioeconomic stress in these men predictably phasic enough during the first 5 months of the calendar year to allow periods of respite for control observation.

The period from April 2 to April 15 was considered by Friedman and co-workers to represent "severe stress," whereas May 14 to May 21 a period of "maximal respite" from stress. In all, 39 accountants participated in the study throughout the entire period. From the data presented by these workers the following are the mean serum cholesterol levels for "Maximal occupational stress" and for "maximal respite";

During "Maximal Occupational Stress," Mean Cholesterol =	230 mg/100ml
During "Maximal Respite," Mean Cholesterol =	222 mg/100ml
Difference	8 mg/100ml

In order to evaluate whether or not dietary changes during these periods might have accounted for the serum cholesterol difference shown above, these workers took a very detailed dietary history for the two critical periods, April 2-9 ("maximal stress") and May 14-21 ("maximal respite") Since so much reliance is placed upon these dietary records by the authors, our first approach must be to accept the dietary evaluations at face value and to determine whether they support the conclusion arrived at that stress itself, rather than dietary changes, was responsible for the observation of a change in mean cholesterol level of 8 mg/100ml The accountants were divided into two groups, depending upon the type of accounting they did. Dietary evaluations were presented by Friedman and associates for

Indeed the dietary changes could readily have accounted for twice the observed changes. In summary, therefore, the conclusion of Friedman and associates that "the present studies indicate an extreme sensitivity of the serum cholesterol to the occurrence of emotional duress described as *socioeconomic stress*" might much better be replaced with the conclusion that accountants eat a little more when they are working long hours and that possibly their cholesterol levels rise a little during such times, in an amount expected from the extent of their dietary change.

What other observations are in the literature which claim to relate stress with serum cholesterol or other lipid levels are no more convincing than those just discussed. No critical evaluation of the quantitative changes observed and the extent to which they can be explained by concomitant dietary alteration is generally presented Thus the singling out of a few persons from a large group who show an appreciable change of serum cholesterol or lipoprotein level during an episode of presumed stress may very well reflect the singling out of the persons from the overall group who are most sensitive to relatively small dietary changes, since it is well known that such persons exist.

No acceptable evidence has yet been presented to suggest an effect of stress upon serum lipoproteins or serum *cholesterol* levels in man that cannot be as well, or better, explained by the solidly-established effects of dietary alterations upon such blood lipids It is to be hoped that some evaluation of the possible factor of stress will be made in the future

the various lipoproteins listed above. This information can, therefore, now be put on a caloric basis as follows:

For a restriction of 10 calories per day, the average fall in lipoprotein levels anticipated are;

1.64 mg/100ml of s_f0-12 lipoproteins
0.44 mg/100ml of s_f12-20 lipoproteins
1.85 mg/100ml of s_f20-100 lipoproteins
2.29 mg/100ml of s_f100-400 lipoproteins

The chemical composition of these lipoprotein classes is known from the work of Lindgren and associates[35]. The s_f0-12 and s_f12-20 lipoproteins contain approximately 34% cholesterol by weight; the s_f20-100 and s_f100-400 contain approximately 13% cholesterol by weight. Therefore, the overall fall in serum cholesterol level corresponding to a 10 calorie per day restriction *would be anticipated to be 1.64x0.34 + 0.44x0.34 + 1.85x0.13 +* 2.29x0.13, or a total of *1.25 mg/100ml.* This is, of course the *average* fall anticipated, some, more sensitive than average, showing a more extensive fall in level, others, less sensitive than average, showing a less extensive fall (even including some with no change or a rise in cholesterol level).

Utilizing this simple estimate (which is extremely unlikely to be off as much as a factor or two), it can be determined how *much the Friedman accountants should have fallen in serum cho-*lesterol level as a result of ingesting 63 fewer calories per day during "maximal respite" than they did during "maximal stress." If *10* calories per day results in a fall of *1.25* mg/*100ml* of serum cholesterol, then 63 calories would be expected to cause a fall of 6.3x1.25, or 7.9 mg/100ml of serum cholesterol. This is to be compared with the 8 mg/100ml fall in cholesterol observed by Friedman and associates. In actual fact, the 8 mg/100ml serum cholesterol fall observed by Friedman is so uncertain, statistically, that it might really be 0 mg/100ml, or as much as 16 mg/100ml, just on a sampling basis alone. The 63 calorie per day *change in dietary consumption for the two periods,* stress and respite from stress, can easily have been from 0 calories to 100 or more calories per day, considering the "strength" of the information provided. *Therefore the dietary changes involved* can easily have accounted for the observed cholesterol changes

ease Coronary heart disease at the sub-clinical level occurs in two types of individuals,

(a) those who have never had an episode of clinical coronary heart disease. They are developing sub-clinical coronary heart disease, some at greater rates, some at lesser rates, and therefore have a greater or lesser risk of evolution of the clinical manifestations in such forms as angina pectoris, myocardial infarction, coronary insufficiency, heart failure or death.

(b) those individuals who have had a clinical manifestation of coronary heart disease in one or another form but who, during the interim period after recovery from a first, second or third clinical manifestation, can again be regarded as being in the sub-clinical phase of the disease awaiting the possibility of a recurrence of the clinical entities.

Both such groups of individuals deserve the attention of the clinician with respect to the prevention of future clinical manifestations of coronary heart disease. Who are these individuals? It has been stressed before that for group (a) *every adult in the population* is a potential candidate for future coronary heart disease Therefore, every adult in the population may be regarded as a proper patient for the treatment of sub-clinical coronary heart disease and prevention of future clinical heart disease. Indeed, unless every adult in the population is regarded as a patient in this sense serious inroads upon the mortality now claimed by coronary heart disease in its various forms will not be made Patients in the second category, group (b), namely those who have already had at least one clinical manifestation of coronary heart disease but who are now in the sub-clinical phase again, are self-evident The vast majority of these will have been under the care of a physician, who, of course, will know that they are again in the sub-clinical phase of coronary heart disease It would be deplorable to consider such patients simply as candidates for watchful waiting until a next episode of clinical coronary heart disease, or to limit advice to them to a statement that no problem exists because they have weathered their acute clinical episode. A great deal should be done for these patients, and can be done without fear of provoking cardiac neurosis Our survey in this book of features associated with

Chapter XV

THE PREVENTION OF CLINICAL CORONARY HEART DISEASE

MANY FACETS of the problems of sub-clinical coronary heart disease and the risk of future clinical manifestations have been taken up in this text. Wherever the information was deemed pertinent to the clinical task of prevention and management of coronary heart disease this was emphasized. It is the purpose of this chapter to pull together much of this information and to indicate to the clinician that an integrated program is possible today with which a highly promising effort can be made to prevent coronary heart disease. The discussions which have preceded this chapter make it abundantly clear that our knowledge of coronary heart disease is not complete. It is doubtful that, for coronary disease or any other disease, knowledge ever will be truly *complete.* But, for any disease, the more facts that are at our disposal, the more we know about the determinants of risk of the disease, the course of the disease, and about agents which influence one or another factors known to be involved in the disease, the more it becomes possible to design a reasonable program for prevention of that disease. So long as the clinician keeps an open mind with respect to the place of additional new laboratory and clinical findings, the preventive program can be modified toward improvement. In the introduction to this book it was stated that the management of clinical episodes of coronary heart disease is well covered elsewhere and is therefore not considered here. What does deserve intensive, practical consideration here is a program for applying extensive knowledge that is available and on a very solid footing toward the end of minimizing the rate of progression of sub-clinical coronary heart dis-

genic Index elevation, have much higher risks of future coronary heart disease than those characterizing an appreciable proportion of the men in the population. It would seem completely unwarranted to exclude these women from our program of preventive management even though it is true that, *on the average*, women have a lower coronary heart disease incidence rate than do men. Going further, one might choose to focus attention upon individuals over 50 years of age since the attack rate of clinical coronary heart disease is much greater above that age than it is, on the average, below that age, and it continues to rise progressively with further increase in age. In one sense concentration upon the over-50 year age group is justified by that fact of a higher attack rate of clinical disease. However, two major considerations militate against this type of approach. First, the incidence of clinical coronary heart disease is alarmingly high for persons below 50 years of age. It is especially desirable to intercept such great prematurity of this disease. Since risks can be predicted long in advance of clinical disease, it would be particularly tragic to allow markedly, excessive risks to go unnoticed and to be productive of manifest coronary heart disease below the age of 50 years. These considerations argue strongly against the exclusion of young adults from the heart disease prevention program. There are the many children who are characterized by massive lipoprotein level elevation because of hereditary defects in lipoprotein transport. Unless some effort is really made to seek them out and to alter their lipoprotein levels, their outlook is distinctly unfavorable. Perhaps an even more cogent consideration in this regard is the fact that all of the evidence concerning the mode of operation of the lipoprotein level and the blood pressure in the production of an excessive rate of development of sub-clinical coronary heart disease points strongly to an accumulative process. The longer this process goes on, the more disease there will be, and, since we cannot count on the exact extent of reversal of established disease that may be possible, this argues strongly in favor of a very early approach, to determine the rate at which sub-clinical coronary heart disease is developing and to intercept its development before the total accumulated disease has become too great. What

increase or decrease in the incidence rate of clinical coronary heart disease has demonstrated that such effects are mediated, in the main, either by the habitual level in the blood of certain *lipoproteins, the* $s_f0\text{-}12$, $s_f12\text{-}20$, $s_f20\text{-}100$, and $s_f100\text{-}400$ lipoproteins, or by the blood pressure, or by both. One factor that has not been treated here is that of coagulability of the blood, and its relationship to at least some of the clinically manifest forms of coronary heart disease. This is no oversight, but rather the result of the sketchiness of real evidence concerning the place of blood coagulability in the development of sub-clinical coronary heart disease. Some aspects of this problem will be considered below.

There is every reason to believe that vigorous attention to these two factors, the blood lipoproteins and the blood pressure, can and will make a real difference in the mortality rate of coronary heart disease. Asymptomatic elevation in blood lipoprotein levels and hence, of Atherogenic Index Value, should not be regarded as innocuous. The *absence* of symptoms characterizes the subclinical phase of coronary heart disease. However, the risk of future clinical manifestations is high with elevation in Atherogenic Index values, and with the passage of time such high risk individuals will experience all-too-many clinical episodes of coronary heart disease. Neither should asymptomatic elevation *of the blood pressure be regarded as benign,* as it has been by some workers, either in men or women. Asymptomatic elevation in blood pressure means, on the average, an increased rate *of accumulation of sub-clinical coronary heart disease* and an ultimate high risk of evolution into one of its serious, or fatal clinical manifestations.

Let us suppose one thinks of potential candidates for prevention of clinical coronary heart disease among adults in the United States population. Since men at most ages show a higher incidence rate of clinical coronary heart disease *than do women,* an initial conclusion would be that preventive medical attention should be centered upon men. To be sure, *the attack rate is* greater in the men so that, in one sense, *they are as a group in* greater need of preventive management. But, there are *many* women who, either because of blood pressure elevation or Athero-

tive prosecution of a program for the prevention of clinical coronary heart disease. At present a major consideration is the low degree of reliability of the values determined by many clinical laboratories, as recently reported[93], to say nothing of the methodology and standardization differences that exist from laboratory to laboratory. But were this the real essence of the difficulty with the application of the blood cholesterol measurement, steps could be taken to improve the existing situation. Methodology could be standardized and valid, reproducible techniques could be learned by essentially all clinical laboratories. However, even perfectly executed, the measurement of the blood cholesterol will fall far short of provision of the requisite information *either* for prediction or for preventive management programs. This does not mean that a blood cholesterol determination is without value Any biochemical measurement, properly performed, has intrinsic value, but the issue of real consequence is whether or not the measurement provides the necessary clinical information It is certainly true that the blood cholesterol level is related to the development of coronary heart disease. Furthermore, during the sub-clinical phase of coronary heart disease elevation of blood cholesterol level is predictive of an increased risk of future clinical coronary heart disease. But, for prediction of risk, even a perfectly executed blood cholesterol determination necessarily leads frequently to an erroneous answer concerning the patient. Why is this so? The lipoproteins which circulate in the blood *all* contain some cholesterol. Indeed the blood lipoproteins are essentially the sole source of what cholesterol is measured in a usual blood cholesterol analysis However, two points concerning the blood lipoproteins and the cholesterol they contain are central to the entire problem. These are the facts that

(1) only *certain* of the blood lipoproteins are important for coronary heart disease

(2) the content of cholesterol differs from the various lipoprotein classes

all this leads up to is the fact that no program can be regarded as medically sound if it falls short of doing two things, providing the earliest possible evaluation of the lipoprotein status and blood pressure status of young adults, preferably in the age bracket of 20-25 years. At this age an appreciable number of individuals with high risk will be discovered. Prevention has meaning for these individuals at that early age. For those who are found to show a low risk during the third decade of life are most likely to retain this favorable status, although in some instances there will be unexpected derangement of the lipoprotein levels and/or of the blood pressure as they grow older. This latter group of individuals deserves a re-check of status at intervals, perhaps, of three to five years throughout adult life

Sphygmomanometry is readily available to every physician in his office. It is of little moment whether he measures blood pressure in a reclining versus a sitting position, or with certain types of tolerance tests. What is important is that some set of reproducible conditions be achieved for the periodic blood pressure check It is evident, of course, that multiple blood pressure determinations will greatly improve the accuracy of placement of an individual on a risk scale with respect to the blood pressure. Very little is solved by the negative statement that blood pressure levels are variable for a single individual due to a variety of circumstances All experienced physicians know that they can, by repeat determination, get to know which persons show significant average trends toward elevation in the blood pressure level

The measurement of the blood lipoprotein levels and the Atherogenic Index value is also routinely available to physicians, performed by methods that have been rigorously evaluated in over 150,000 determinations No doubt some clinicians will wonder whether one of the more simple blood lipid measurements might not serve as well as a determination of the actual lipoproteins involved in the development of coronary heart disease. One such that comes into consideration is the determination of the blood cholesterol level Numerous major reasons exist which make it evident that such a determination of the blood cholesterol level will not provide the requisite information for the effec-

Using some representative numbers, consider one person with 400 mg/100ml of the high density lipoproteins and another with 200 mg/100ml of these lipoproteins, all other lipoprotein classes being equal. Since the high-density lipoproteins are 13% cholesterol by weight, the person whose blood shows 400 mg/100ml of high density lipoprotein will have 400x0.13, or 52 mg/100ml of cholesterol in the blood in this form. The person with 200 mg/100ml of high-density lipoprotein will have 200x0.13 = 26 mg/100ml of cholesterol in the blood in this form. The blood cholesterol analysis will show the former person to be 26 mg/100 ml higher than the latter and would predict the former person to have a higher risk of coronary heart disease, when in fact the s_f0-400 lipoproteins may be identical in level, the Atherogenic Index values are therefore identical, and the predicted risk of coronary heart disease will be identical.

A much more serious error can arise in another way through reliance upon the blood cholesterol level without knowledge of the lipoprotein distribution Suppose two men at age 35 years are considered with the following lipoprotein distributions:

	Case A	Base B
s_f0-12	400 mg/100ml	400 mg/100ml
s_f12-20	50 mg/100ml	50 mg/100ml
s_f20-400	300 mg/100ml	100 mg/100ml
High Density Lipoproteins	100 mg/100ml	300 mg/100ml

The s_f0-20 lipoproteins are approximately 34% cholesterol by weight, the s_f20-400 lipoproteins, 13% cholesterol by weight, and the high-density lipoproteins, 13% cholesterol by weight. These three classes together provide almost all of the blood cholesterol Therefore, for case A, the blood cholesterol is (450) x (0.34) plus (300) (0.13) + 100 (0.13), which is 205 mg/100ml For case B, the blood cholesterol is (450) (0.34) + (100) (0.13) + 300 (0.13), which is 205 mg/100ml Therefore, on the basis of blood cholesterol determination Case A and Case B would be stated to have identical risks of coronary heart disease. Now, the Atherogenic Index may be calculated for both cases. For Case A the Atherogenic Index is (1.0) (400) + (1.75) (350) over 10, or 101 units. For Case B the Atherogenic Index is (1.0) (400) + (1.75) (150) over 10, or 66 units.

THE IMPORTANCE OF THE FACT THAT ONLY CERTAIN LIPOPROTEINS ARE INVOLVED IN CORONARY HEART DISEASE

The blood lipoproteins can be broadly characterized as belonging to three major groups:

(a) *The s_f0-400 band of lipoproteins, of demonstrated importance for coronary heart disease* (See Chapter III)

(b) The very large lipoproteins from s_f400 out to the *chylomicrons. For the human these have not been demonstrated to be of importance for coronary heart disease, although it has not been demonstrated that they are innocuous.* Fortunately such lipoproteins are not often very high in level,* and secondly their levels correlate so highly with those of the s_f100-400 class that information concerning them is available when the s_f100-400 class is measured.

(c) The high-density lipoproteins, which are comparable, in part, to those referred to as alpha-lipoproteins by techniques other than ultracentrifugation. Such lipoproteins are definitely *not* elevated in level in coronary heart disease In fact, what data are available indicate that they are depressed slightly in level in coronary heart disease[94, 95].

The major goal of a blood lipid measurement with respect to prediction of coronary heart disease risk is to assess the amount of lipid in the blood in the form of lipoproteins in the flotation classes between s_f0 and s_f400 It was stated above that the high-density lipoproteins are unimportant for coronary heart disease. However, these lipoproteins *do contain* cholesterol to the extent of approximately 13% by weight There is considerable variation from one person to another in the level of these high-density lipoproteins, and they are almost completely independent of the level of the various lipoprotein classes from s_f0 to s_f400. Therefore, it is readily possible to find two humans of the same age and sex, in one of whom the high-density lipoproteins are twice as high in level as in the other but where every lipoprotein *from s_f0 to s_f400 is the same for* both persons.

*In experimental animal studies, e g in the rabbit, the very large lipoproteins are innocuous with respect to arteriosclerosis development in comparison with those comparable in size with human s_f0-400 lipoproteins

	Case 1 (mg/100ml)	Case 2 (mg/100ml)	Case 3 (mg/100ml)
Cholesterol Contributed From High Density Lipoproteins	300x0.13=39	300x0.13=39	300x0.13=39
From s_f12-20 Lipoproteins	60x0.34=20	60x0.34=20	60x0.34=20
From s_f0-12 Lipoproteins	400x0.34=136	300x0.34=102	200x0.34=68
From s_f20-400 Lipoproteins	100x0.13=13	200x0.13=26	300x0.13=39
Total Blood Cholesterol	208	187	166
Atherogenic Index	63 units	76 units	83 units

Here the paradoxical situation arises that the cholesterol, dropping successively from Case 1 to Case 3 predicts erroneously a successively lower risk of future clinical coronary heart disease, whereas the Atherogenic Index, rising successively from Case 1 to Case 3 predicts a successively higher risk of future clinical coronary heart disease. The source of erroneous prediction from the cholesterol measurement arises from the shift of lipoproteins relatively rich in cholesterol to lipoproteins relatively poor in cholesterol content. Hence the cholesterol level falls. However the cholesterol-poor s_f20-400 lipoproteins are even more important, milligram for milligram, than the s_f0-12 lipoproteins. Hence it is possible to have the Atherogenic Index rise as the cholesterol level falls! Levels such as are shown for Case 1 and Case 3 can be seen in a single individual during therapy. Suppose that a man started with a distribution of lipoproteins identical with that of Case 1. If a regimen of a low animal fat, high carbohydrate diet were instituted, the s_f0-12 lipoproteins will fall, in general, and the s_f20-400 lipoproteins will rise. Cases have been observed where these changes could convert a distribution such as that of Case 1 to that of Case 3. Thus the cholesterol measurement before and after institution of the dietary therapy would indicate, erroneously, a favorable response, whereas the lipoprotein Atherogenic Index measurement would indicate an unfavor-

The risk evaluation from Table XV is that the man with the Atherogenic Index value of 101 units has 14.2 over 3.24, or 4.4 times the risk of future clinical coronary heart disease that characterizes the man with an Atherogenic Index of 66 units. Thus in these two cases the blood cholesterol measurement (even if performed perfectly) is off 4.4 times in its prediction of equal risk for the two men whose cholesterol levels are both 205 mg/100ml. This cholesterol level of 205 mg/100ml is a relatively low one. Hence, a favorable prediction would be made on this basis. Yet one of the two men described with this cholesterol level has a highly unfavorable outlook and is in need of preventive medical management, a fact which would be lost sight of entirely if attention were focussed upon the low cholesterol level

THE IMPORTANCE OF THE FACT THAT LIPOPROTEINS DIFFER IN CHEMICAL COMPOSITION

In the illustrations above the obscuring effect of the high-density lipoproteins upon the prediction via blood cholesterol measurement was described Another type of difficulty operates to lead to erroneous prediction through blood cholesterol measurement, namely the differing chemical composition of lipoproteins within the s_f0 to s_f400 band. Three men may be considered with identical levels of the high density lipoproteins, e g. 300 mg/100ml Now, various possible (and observed) combinations of s_f0-12, s_f12-20, and s_f20-400 lipoproteins may be considered. Suppose for simplification s_f12-20 remains at 60 mg/100ml for all the cases to be analyzed. Suppose further that for *s_f0-12 plus s_f20-400, there is a total of 500 mg/100ml Three* distributions within this level of 500 mg/100ml will illustrate *the problem* Let the *first case* (Case 1) have s_f0-12 = 400 mg/100ml and s_f20-400 = 100 mg/100ml; the second case (Case 2), have s_f0-12=300 mg/100ml and s_f20-400=200 mg/100ml, and the third case, (Case 3), have 200 mg/100ml of s_f0-12 lipoproteins *and 300 mg/100ml of s_f20-400* lipoproteins Now from chemical composition data for the various lipoproteins, the blood cholesterol can be calculated for cases 1, 2, and 3 and from the s_f0-12, s_f12-20, and s_f20-400 the Atherogenic Index is calculated.

genic Index should be lowered. These are hypothyroidism and diabetes mellitus.

Hypothyroidism should be searched for carefully, and should be treated effectively where present, for the elevation of s_f0-12 and s_f12-20 lipoproteins means an elevation in the Atherogenic Index and, thereby, an increase in the risk of clinical coronary heart disease. Fortunately, therapy with desiccated thyroid substance, thyroxine, or tri-iodo-thyronine is specific therapy and will effect a lowering in lipoprotein level as a concomitant of correction of the hypothyroidism Some patients present more occult problems referable to the thyroid status Where clinical hypothyroidism is suspected as a possible diagnosis and where s_f0-20 lipoproteins are elevated, but where other laboratory measurements of thyroid function are equivocal, a trial of thyroid therapy is clearly indicated There are, further, a large number of persons in the population who, at one time or another, have had ablative treatment of their thyroid gland by surgery, radiation, or by chemical means To be sure, frank clinical myxedema is not a common residual effect of surgical treatment of hyperthyroidism Nevertheless persons who have had ablative therapy to their thyroid may suffer elevation of s_f0-12 and s_f12-20 lipoprotein levels Even in the absence of clinical hypothyroidism such persons deserve a trial of thyroid replacement therapy.

Diabetes mellitus presents the second special situation of real consequence Of course, first of all diabetes itself must be controlled clinically Thereafter attention must be directed toward any excessive risk of coronary heart disease a particular diabetic may have as a result of lipoprotein-Atherogenic Index elevation The discussion of diabetes in Chapter XII and the data of Table XLV indicate strongly that chemical control of diabetes (even within the clinical state free of acidosis) is of real importance in determination of the lipoprotein status. Therefore, within the limits imposed by patient intelligence, life circumstances, and the prevention of hypoglycemic episodes, hyperglycemia and glycosuria should be minimized The evidence in Table XLV gives the average improvement in Atherogenic Index values with increase in the control of hyperglycemia. It follows that some diabetics will experience much greater than average

able response, which is correct. The use of the familiar rice diet is a case in point, where precisely this type of situation arises *and where the blood cholesterol would indicate the direction of the response* *opposite* to what is truly occurring in the patient. Probably the major reason why this type of patient on a rice diet does not fare as badly, on the average, as the Atherogenic Index trends would suggest, is that the rice diet regimen as practised is associated with a favorable fall in diastolic blood pressure.

THE PLANNING OF A PREVENTIVE REGIMEN FOR INDIVIDUAL PATIENTS

For those patients whose overall risk of coronary heart disease is low or moderate, *when calculated by multiplication of the* risk arising from Atherogenic Index value by that arising from diastolic blood pressure, the best program is simple notification of the patient that he is a fortunate person characterized by a low risk of future coronary heart disease. No specific measures are indicated. Where the overall risk is elevated, from elevated blood pressure with or without Atherogenic Index elevation, it is definitely indicated that a program be directed toward lowering such elevated blood pressure. This is true even though the blood pressure elevation is asymptomatic at the time of study. The entire subject of the most efficacious procedures for controlling elevation in blood pressure is a major subject in itself, a subject covered elsewhere in sources available to physicians. Where the risk is elevated from elevation in Atherogenic Index with or without diastolic blood pressure elevation, there is a definite indication for a program directed toward the lowering of the elevated Atherogenic Index values. The approach to this problem for an individual patient deserves amplification.

THE PROGRAM FOR LOWERING ELEVATED ATHEROGENIC INDEX VALUES

Special Situations

Two special situations must be commented upon before consideration of the person in the population-at-large whose Athero-

DIETARY APPROACH TO ATHEROGENIC INDEX LOWERING IN THE OVERWEIGHT PERSON

The overweight person shows, on the average, an appreciable elevation of the Atherogenic Index value (See Chapter IX). Further in those overweight persons who demonstrate elevation in blood lipoprotein levels and Atherogenic Index values the correction of overweight via a decrease in habitual calorie intake provokes a fall in Atherogenic Index value, which is maintained if the person does not return to his habitually high calorie intake. The "natural" experiment described in Chapter IX provides us with very reasonable working data for the clinician to use in planning a regimen for the overweight person. Under the usual circumstances of living, a cross-section of individuals, described in Chapter IX, either lost or gained weight spontaneously during a one to two year period The lipoproteins and Atherogenic Index increased, on the average, for those who gained weight and decreased on the average for those who lost weight. From these data the average changes in level that can be anticipated for the various lipoprotein classes and for the Atherogenic Index value per unit change in daily calorie intake were calculated (See Chapter XIV) These values are as follows;

For a reduction of 10 calories per day in habitual caloric intake, *on the average*,

S_f 0-12 lipoprotein levels fall	1.6 mg/100ml
S_f 12-20 lipoprotein levels fall	0.4 mg/100ml
S_f 20-100 lipoprotein levels fall	1.8 mg/100ml
S_f 100-400 lipoprotein levels fall	2.3 mg/100ml
Atherogenic Index Values fall	0.95 units

The clinician may utilize such data directly in planning a long-term regimen for the overweight person. This may be illustrated by consideration of a specific case of an overweight man of 35 years of age whose Atherogenic Index value is 120 units, a value that corresponds to an appreciable elevation in risk of future clinical coronary heart disease. The physician would be desirous of lowering such a value to 80 Atherogenic Index units, if possible, or perhaps more What caloric restriction is needed? If 10 calories per day corresponds to an average lowering in Atherogenic Index of 0.95 units, then the required caloric restriction

effects upon Atherogenic Index value, others, much lesser effects. The clinician can readily determine this in specific patients directly. *For those patients where more rigid control produces* large drops in Atherogenic Index values, advantage should be taken of this. For those where the effect of control rigidity upon Atherogenic Index is minor, the clinician may decide to relax control measures appreciably.

General Cases

We come now to the general case of the person in the population-at-large whose Atherogenic Index is elevated and who is in need of medical management to lower the elevated value. This person is free of such known metabolic disorders as hypothyroidism or diabetes mellitus which bring in special considerations. A program of preventive medical management is needed for this person in the population-at-large. At the present time and with the knowledge now available to us, dietary measures are first in importance, in part because of the widespread confirmation of their efficacy in achievement of Atherogenic Index lowering and in part because the dietary approach has so relatively few unknowns in the form of side effects that may characterize pharmaceutical approaches Where dietary measures fail to produce the desired effects upon blood lipoproteins, either because the patient is metabolically unresponsive or because he is uncooperative with respect to the dietary measures, there do now exist certain pharmaceutical agents to bolster the physician's armamentarium in this field Further pharmaceutical research, on a large-scale, is urgently to be encouraged, for it is entirely reasonable to believe that an ultimate replacement of dietary by pharmaceutical methods is possible. The dietary approach is best analyzed if patients are first categorized into those who are overweight and who should lose weight and those who are either at ideal weight or are underweight, in which cases weight loss is undesirable

the calories that must be restricted either in the form of animal fat or carbohydrate (depending upon the lipoprotein distribution) by calories in the form of one of the innocuous vegetable oils

DIETARY APPROACH TO LOWERING OF ATHEROGENIC INDEX VALUES IN PERSONS AT IDEAL WEIGHT OR BELOW IDEAL WEIGHT

It has been adequately stressed that lipoprotein level and Atherogenic Index elevation are by no means limited to the overweight person. Both may occur in persons at ideal weight or in persons who are underweight Calorie restriction will, therefore, be out of the question in these cases, in general But calorie restriction is *not* essential to achieve lipoprotein lowering It was shown in the discussion of Chapter X that alteration in the *source* of calories can provoke marked lowering of lipoproteins. From the data of Tables XXXVIII and XXXIX the following average responses can be estimated,

For every gram per day of animal fat* restricted, on the average,

S_f0 12 lipoprotein levels fall	1 3 mg/100ml
S_f12 20 lipoprotein levels fall	0 25 mg/100ml
S_f20 100 lipoprotein levels fall	negligibly
S_f100 400 lipoprotein levels fall	negligibly

Similarly, for every gram per day of carbohydrate restricted, on the average,

S_f0 12 lipoprotein levels fall	negligibly
S_f12 20 lipoprotein levels fall	negligibly
S_f20 100 lipoprotein levels fall	0 1 mg/100ml
S_f100 400 lipoprotein levels fall	0 35 mg/100ml

With the knowledge of the patient's lipoprotein distribution, the dietary alterations can be prescribed by the physician as developed in the following illustrative examples.

If a patient at ideal weight or below is characterized primarily by elevation in S_f0-12 and S_f12-20 lipoprotein levels, restriction

*[illegible]

From

value

to reduce the Atherogenic Index by 40 units is (40 over 0.95)x10, or 421 calories per day. Many overweight patients can well afford to ingest 421 fewer calories per day. The *maintenance* of the average drop of 40 units in Atherogenic Index value requires that *this person's habitual caloric intake remain 421 calories per day* fewer than before therapy. Whether a physician chooses to reduce weight in overweight patients rapidly or slowly is his *own choice, but the important issue here is that over the long* term this patient must still average 421 calories fewer per day to maintain the lowered Atherogenic Index value.

This is how the physician can start with *the management of* the overweight patient. Of course, few patients are precisely average in their response. Therefore with a caloric restriction of 421 calories per day, *some will show even a more marked* drop in Atherogenic Index than the calculated 40 units, others a lesser response. No substitute for direct checking of response in each patient is currently known If the response is much better than average for a particular patient, then the physician may wish to liberalize the regimen and make the habitual caloric restriction less than 421 calories per day. If the response is poorer than average, then two possible considerations arise:

(1) the patient simply is not responsive to dietary measures, or

(2) the patient needs more specific dietary measures than mixed calorie restriction.

The calculated responses to calorie restriction are for *mixed* calorie restriction in persons with usual distributions of the various lipoprotein classes which contribute to the Atherogenic Index. Since it is known that the S_f0-12 and S_f12-20 lipoprotein levels are lowered by restriction of animal fat and saturated vegetable fat and that S_f20-100 and S_f100-400 lipoprotein levels are lowered by carbohydrate restriction, the physician can take advantage of these facts either in the overweight patient, the ideal weight patient, or the underweight patient For example, the physician may be dealing with an overweight patient for whom he considers a habitual reduction of 421 calories per day as too much. In this case, by specific attention to that patient's lipoprotein distribution, the physician may choose to replace some of

drate can be replaced by one of the acceptable vegetable oils, without fear of elevation of any lipoprotein classes.

These are the general principles which can guide the physician in planning a dietary regimen. At all times it must be borne in mind that the particular patient's sensitivity to the various dietary factors is the ultimate guide for that patient. But the general principles can be utilized to initiate the program of prevention. These dietary alterations neither require liquid, formula diets nor unpleasant fad dieting. Endless variety is possible and is available for specific planning of kitchen-tested menus and recipes within the framework of these dietary principles.* Nor is there any indication to deviate from the sound nutritional principles concerning adequacy of protein, mineral, and vitamin intake. The concern over deficiencies that might be encountered in alteration of diets is most commonly encountered from sources with little or no experience with dietary alteration. Probably it would be best to refer to the diets to be utilized as "altered" diets rather than "restricted" diets, for extensive experience with patients indicates that they are hardly experiencing any real restrictions when they alter their diet to one consistent with an effort to prevent coronary heart disease.

PHARMACEUTICAL APPROACHES TO THE LOWERING OF ELEVATED LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES

Dietary methods are highly effective in the lowering of lipoprotein-Atherogenic Index values. Yet, even with careful application of the dietary methods available, there will still be three classes of patients who present a problem. These are: (a) the patients who will *not* adhere to the dietary program even though its efficacy has been demonstrated, (b) the patients who respond to diet but who are *still* in need of more extensive Atherogenic Index lowering, and (c) the patients who respond poorly to dietary measures. For all these individuals, the availability of measures to supplement the dietary approach would be highly wel-

***Dietary Prevention and Treatment of Heart Disease*, by John W. Gofman, Alex V. Nichols and E. Virginia Dobbin. G. P. Putnam's Sons, 1958

of animal fat is indicated. *Suppose a patient shows an* s_f*0-12* level of 550 mg/100ml and an s_f12-20 lipoprotein level of 80 mg/100ml and that the physician would like to achieve a 20% lowering of both, that is a lowering of s_f0-12 lipoproteins to 440 mg/100ml and a lowering of s_f12-20 lipoproteins to 64 mg/100ml. *The lowering of animal fat intake for this extent of* s_f*0-12 lipo-*protein level lowering is calculated as 110 over 1.3, or 84.6 grams per day on a habitual basis Many Americans consume considerably more than this amount of animal fat per day; others do not. If this much animal fat is available for restriction, a corresponding weight of any of several vegetable oils, such as corn oil, cottonseed oil, peanut oil, or safflower oil can be incorporated in the diet, thus averting *any* caloric loss and, hence, any weight loss. Since these calculations are for *average* patients, the physician will be very pleased with the much greater lipoprotein response in some patients, and will realize that this approach alone is inadequate for certain other patients.

If a patient at ideal weight is characterized by elevation in s_f20-400 lipoproteins, the indications are in the direction of carbohydrate restriction. *The data indicate a lesser sensitivity of* s_f20-100 lipoproteins to carbohydrate restriction than that for s_f100-400 lipoproteins Whether this is generally true or whether it represents a feature of this particular group of subjects is not known. As a reasonable approximation, it can be estimated that s_f*20-400 lipoproteins as an overall group fall some 0.2 mg/100ml* per gram of carbohydrate per day Suppose the s_f20-400 lipoprotein level is high and it is desired to achieve a reduction of 50 mg/100ml. The required restriction of carbohydrates is 50 over 0.2, or 250 grams per day This is an appreciable reduction in carbohydrate intake per day, and one not readily achieved in some patients. Fortunately, however, patient with marked elevation in s_f20-400 lipoprotein levels are *much* more sensitive than average to the effect of carbohydrate and will show much more marked drops in level than the 0 2 mg/100ml per gram of dietary carbohydrate estimated above For them modest carbohydrate restriction will provoke appreciable falls in s_f20-400 lipoprotein levels. In other patients the effect of carbohydrate restriction will be much less. The calories lost from carbohy-

istration. On the other hand, the asymptomatic, relatively youthful person with marked elevation in lipoprotein levels can be treated with thyroid substance under observation, without any undue fear that unmanageable side reactions will develop. In those unusual cases where real evidence of intolerance develops, this fact itself decides the issue. Thyroxine or tri-iodothyronine are also effective in reduction of elevated lipoprotein levels[80, 81]. There appear to exist few major features which would differentiate these, with respect to efficacy, from desiccated thyroid substance. There is no reason known at this time why thyroid administration cannot be used as a supplement to dietary measures.

Estrogenic Hormones

Interest in estrogenic hormones as possible pharmaceutical agents for reduction in elevated lipoprotein levels has been widespread[96, 97, 98, 99]. There has existed no doubt concerning efficacy of estrogenic substances in effecting reduction in blood lipoprotein levels for some time now. However, in many of the studies the dosage levels employed were relatively enormous, with the result that side reactions of sufficient severity were induced as to discourage further consideration of this class of substances by many physicians. However, certain of the studies have been carried out at more modest dosage levels, with favorable effects upon blood lipoproteins[99, 100]. One of these is a very long-term study of the administration of ethinyl estradiol to male myocardial infarction survivors. In that study, Marmorston, Moore and their associates have endeavored to adjust the dosage of ethinyl estradiol, during the study, for each patient in an effort to "titrate" the patients so that side reactions such as gynecomastia and loss of libido could be minimized or avoided entirely. The median dose of ethinyl estradiol in their series of patients has been 100 micrograms per day, administered orally. These eighteen patients had been treated at least for 90 days. The effect of ethinyl estradiol administration after 90 days showed several remarkable features. Significant reductions occurred in mean level of all four lipoprotein classes, S_f0-12, S_f12-20, S_f20-100, and S_f100-400. For the S_f12-20, S_f20-100, and S_f100-400 lipopro-

come. Myriads of pharmaceutical agents have been proposed for *accomplishment of this task; few have proved to have any* merit. But these few that have shown merit, in that lipoprotein levels can often be reduced through their use, deserve specific *comment here.*

Thyroid Substance

Desiccated thyroid substance has been conclusively shown to be capable of provoking lipoprotein and Atherogenic Index lowering in euthyroid persons. (See discussion in Chapter XIII). *In the euthyroid adult the usual ultimate requirement for maintenance* of a suppression of Atherogenic Index values is a dose of 3 grains or more per day of USP desiccated thyroid substance. Smaller doses *ultimately allow for "escape" mechanisms to operate*, as previously discussed. There does appear to be some virtue in building the thyroid dosage up relatively slowly, on a schedule such as *one grain per day for two weeks, then two grains per* day for two weeks, then three grains per day for four weeks At this point, a determination can be made of the efficacy of the program by an analysis of the blood lipoproteins If inadequate, then the dose should be increased to four grains per day for one to two additional months, with subsequent blood lipoprotein determination. Many physicians have maintained large numbers of patients on doses of four or more grains of thyroid substance per day over periods of years Thyroid substance most uniformly affects the s_f0-12 and s_f12-20 lipoprotein levels, although less regularly it can also provoke marked lowering of s_f20-100 and s_f100-400 lipoprotein levels The relationship between extent of drop in levels with initial lipoprotein level is marked for all the lipoprotein classes (See Chapter XIII)

The problem of wisdom of use of an agent such as desiccated thyroid substance for the purpose of achievement of Atherogenic Index reduction is one where individual clinical judgments will differ widely As emphasized before, the selection of candidates for the use of thyroid substance should in large measurement help determine the physician's attitude The patient with severe, symptomatic clinical coronary disease in the form of angina pectoris is not likely to be considered for a trial of thyroid admin-

mittent anticoagulation, a combination of these effects, or by some wholly separate mechanism needs further elucidation.

Other Pharmaceutical Agents

Beta-sitosterol[105, 106, 107] and nicotinic acid[108, 109, 110] have been studied by several workers with respect to effectiveness in reduction of serum cholesterol levels Adequate data concerning effects upon the various lipoprotein classes are not currently available. Farquahar has suggested that beta-sitosterol probably lowers the S_f0-10 lipoprotein class, but no direct data were presented to substantiate this Unfortunately many studies with agents such as the sitosterols suffer from the failure of the investigators to control the variable of diet. To what extent sitosterols are effective in lowering blood lipids and to what extent they are reflecting an altered dietary composition during their administration is by no means clear. It is to be hoped that definitive evaluation of the lipoprotein response to nicotinic acid in the dosage range of 3 to 6 grams per day will soon be available. Nicotinic acid amide is reported to be without effect upon blood lipid levels.

teins, the effect of estrogen administration was more marked for those showing initially high levels of these lipoprotein classes. In the men with moderate or low levels of these lipoprotein classes, there appeared to be little effect of the estrogen administration. From the point of view of clinical application, this is a favorable finding, since it is precisely those individuals with the highest initial levels who are in greatest need of an agent to lower the levels. The relationship of response with initial lipoprotein level is analogous to that observed in the case of thyroid administration. The magnitude of reduction in lipoprotein levels and Atherogenic Index values in the Marmorston-Moore study is very large, and hence most promising. Should the longer-term followup continue to indicate such large effects, and should the side reactions be of sufficiently low intensity, ethinyl estradiol in the dosage range used by these workers may prove to be a most valuable pharmaceutical aid in lowering elevated lipoprotein levels in men Studies are in progress in women.

Heparin

Parenteral heparin administration is known to provoke an acute fall in the level of S_f12-400 lipoprotein levels[101, 102, 103] This fall is the result of the activation in vivo by heparin of a lipoprotein-lipase which effects the hydrolysis of triglyceride contained in these lipoprotein classes. Unfortunately, however, the enzyme seems to remain activated approximately as long as appreciable heparin activity is present. Thus a single intravenous injection of sodium heparin can effect lipoprotein level reduction for a period of several hours Subcutaneous injection of heparin will extend such periods considerably, but even in this case a single injection will depress S_f12-400 lipoprotein levels for a period less than 24 hours. In a separate study of mortality among patients with established clinical coronary heart disease, Engelberg has reported a highly significant effect of intermittent, subcutaneous heparin administration in the reduction of mortality over a two-year period in comparison with a placebo-treated control series[104]. Whether or not the reported mortality decrease operates via the intermittent reduction in lipoprotein level, via inter-

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CONCLUSION

Coronary heart disease has been considered here in the light of modern laboratory and clinical evidence. A reasonably consistent and integrated concept of some of the major aspects of this disease has, it is hoped, been developed. This concept leads to a suggested program of positive measures that may be considered for the initiation of a program for the prevention of coronary heart disease during its sub-clinical phase, so as to minimize the risk of its evolution into the full-blown, clinical entity. The available knowledge is far from complete With enormous progress in further clarification, there will still remain significant voids in our knowledge. But, today, an integrated framework of evidence does suggest that further delay in the application of a great fund of knowledge is no longer indicated. Therapeutic nihilism is not the equivalent of a justifiable and well-founded conservatism in medicine. To be sure, views will change as new evidence develops. The major features, however, of the knowledge upon which a program of prevention is suggested are very solidly grounded and will not change appreciably. It is not intended that biochemical or biophysical approaches to the management of sub-clinical coronary heart disease be in any way considered as a replacement for the physician caring for a patient as a human Rather such approaches are intended to strengthen *the scientific basis underlying the clinician's approach to this* very serious medical problem. So long as the physician can assure himself that the application of modern concepts to prevention of coronary heart disease will not be harmful and that a strong body of evidence indicates a very great likelihood that such application will be helpful, it hardly could be considered radical *to start now* rather than to wait for complete agreement by everyone concerning every facet of this disease.

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Chapter

12

HYPERTENSIVE RETINOPATHY

BRIGHT[1] pointed out in his communication of 1836 that impairment of vision may be a symptom of renal disease. The visual defect may be due to various causes. Amaurosis occurs as a manifestation of hypertensive encephalopathy (p. 348), the refracting media, fundus and pupillary reflexes being normal Hemorrhage into the retina, the media or the subconjunctival tissues may occur. Unusual cases of visual defects in hypertensive and arteriosclerotic patients are closures of the central artery or vein or large branches. But far more important than these vascular accidents are the peculiar retinal changes first observed anatomically by Tuerck[2] in 1850, ophthalmoscopically by Heymann[3] in 1858, and termed albuminuric retinitis by Liebreich.[4]

The term albuminuric retinitis has been used almost universally until within recent years. It is, however, inappropriate and should be discarded for the following reasons:

1. The retinal lesions in question are not closely correlated with albuminuria. In the nephroses, in which albuminuria is at a maximum, the retinal changes do not occur and are unusual in the nephrotic type of glomerulonephritis. In the end stages of glomerulonephritis and essential hypertension, where the retinal lesions are most common, albuminuria may be slight and occasionally even absent. There is thus no necessary connection between proteinuria and retinal lesions in Bright's disease.

2. The lesions in the retina are not inflammatory in nature but result from circulatory or metabolic disturbances The use of the word retinitis is therefore objectionable.

The available evidence indicates that the retinal lesions formerly included in the concept of "albuminuric retinitis" groups together three pathogenetically distinct types of retinopathy These will be designated in accord with the essential factor in their pathogenesis:

retinal changes.

2. *Arteriosclerotic Retinopathy* —In chronic Bright's disease there occur retinal lesions which result from retinal arteriosclerosis While hypertension is most often present in these cases, the same lesions may result from arteriosclerosis in the absence of elevated blood pressure

3. *Diabetic Retinopathy* —There is a form of retinal change specifically due to diabetes Because this retinal change is often associated with

proteinuria, edema and the other features of the Kimmelstiel-Wilson syndrome, it was formerly included in "albuminuric retinitis." However, diabetic retinal lesions have no necessary correlation with proteinuria, *hypertension or renal insufficiency* and often precede the latter in the ... [illegible] ielstiel-Wilson syndrome. Diabetic

[illegible] same changes in the *retinal arteries* may be present, these will be discussed first.

The Retinal Arteries in Hypertension.—In at least the large majority of instances of pronounced hypertension, the elevated blood pressure is

[illegible]

able because it was made before the days of the sphygmomanometer. In the vast majority of patients with marked hypertension, the retinal arteries reveal one or more of such changes as narrowing, irregularity of lumen,

[illegible]

changes in the retinal arterioles in every one of 80 patients with uncomplicated essential hypertension Wagener[8] pointed out that the initial changes in the retinal arteries in hypertension are narrowing, pallor of the entire width of the arterial blood column and accentuation of the reflex stripe In the experience of the writer, it has been rare that the retinal arteries of a patient with pronounced hypertension are not narrowed. Often, indeed, indubitable, and sometimes pronounced, narrowing of the retinal arteries is present in youthful sufferers from essential hypertension in whom the elevation in pressure is but modest and even intermittent. The attenuation of the retinal arteries persists in hypertensives in whom the blood pressure has fallen after myocardial infarction. In severe hypertension the narrowing is generally immediately obvious. But in less marked hypertension the attenuation of the arteries may be only slight In estimating the caliber of the retinal arterioles, they should be carefully compared to corresponding veins Normally, the artery is about two-thirds to three-quarters as broad as the vein. However, one must be sure that the artery and the vein actually correspond; often an artery is accompanied by two veins or vice versa or the branching different—all of which vitiate the comparison In old age the arteries are often narrow in the absence of hypertension

Both increased tone and arteriosclerotic thickening of the walls may participate in the thinning of the arterial blood columns in hypertension. *Dissociation* of the contribution of these factors in the individual case may be difficult or impossible The nature of the case and the presence or absence of other evidence of retinal arteriosclerosis may help decide.

Chapter

12

HYPERTENSIVE RETINOPATHY

BRIGHT[1] pointed out in his communication of 1836 that impairment of vision may be a symptom of renal disease. The visual defect may be due to various causes. Amaurosis occurs as a manifestation of hypertensive encephalopathy (p. 348), the refracting media, fundus and pupillary reflexes being normal. Hemorrhage into the retina, the media or the subconjunctival tissues may occur. Unusual cases of visual defects in hypertensive and arteriosclerotic patients are closures of the central artery or vein or large branches But far more important than these vascular accidents are the peculiar retinal changes first observed anatomically by Tuerck[2] in 1850, ophthalmoscopically by Heymann[3] in 1858, and termed albuminuric retinitis by Liebreich.[4]

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The available evidence indicates that the retinal lesions formerly included in the concept of "albuminuric retinitis" groups together three pathogenetically distinct types of retinopathy These will be designated in accord with the essential factor in their pathogenesis.

1. *Hypertensive Retinopathy.*—The classical picture of "albuminuric retinitis" occurs only in the presence of hypertension It will be seen in the following that hypertension is the essential factor in the pathogenesis of the retinal changes.

2. *Arteriosclerotic Retinopathy*—In chronic Bright's disease there occur retinal lesions which result from retinal arteriosclerosis. While hypertension is most often present in these cases, the same lesions may result from arteriosclerosis in the absence of elevated blood pressure.

3. *Diabetic Retinopathy.*—There is a form of retinal change specifically due to diabetes. Because this retinal change is often associated with

to demonstrate retinal lesions (hypertensive retinopathy and arteriosclerotic retinopathy) in 25 of 32 cases. Hypertensive retinopathy has been present in almost every instance of the malignant phase of essential hypertension that I have observed (see p. 827). In chronic cases the different [illegible] good accord, statistics as to the fr[illegible]
for here the process us[illegible]
moscopic fin[illegible] In [illegible]
retinopathy
the figures gi[illegible]
used. Thus, in cases [illegible]
cent and Hornicker[21] more than 50 [illegible]
if one studies the eye-grounds care[illegible]
proportion of the severe cases of [illegible]
medical wards show at least such [illegible]
margins of the disk or narrowing of the arteries. But the proportion of cases of acute glomerulonephritis that develops the typical picture of [illegible] small. I am not aware of any comprehensive

of
pr[illegible]
[illegible] tendency to retinal detachment than in other forms [illegible]

phase of essential hypertension. The youngest case reported [illegible] one observed by Bull,[22] a girl, aged five years

The experimental production of hypertensive retinopathy is discussed below (p. 376)

Ophthalmoscopic Findings in Hypertensive Retinopathy.—The fully de-

of all these changes re[illegible]
characteristic picture,

lesion is developing We shall first consider individually the findings in each of the above-mentioned structures

The Papilla—Apart from the antecedent contraction of the arteries, swelling of the nerve head is the first change to be observed in a high

the disk becomes edematous, or the patient may succumb without obvious changes in the papilla. The disk is swollen, has indistinct margins and is

Narrowing of the retinal arterioles in acute glomerular nephritis or the toxemia of pregnancy is doubtless due to increased tone. The same is probably true of uniform narrowing unaccompanied by other changes in essential hypertension.

The signs of retinal arteriosclerosis are described in conjunction with arteriosclerotic retinopathy (p. 382).

I. HYPERTENSIVE RETINOPATHY

These retinal lesions are so called because they occur only in the presence of hypertension, are more apt to develop the higher the diastolic pressure, *and tend to improve or disappear if the blood pressure falls either* spontaneously or as a result of treatment. Such disappearance of the retinal lesions after fall in pressure occurs especially dramatically after successful sympathectomy or removal of a suprarenal tumor.

Occurrence.—Hypertensive retinopathy occurs in those forms of Bright's disease which are marked by arterial hypertension. It is, therefore, not found in focal nephritis, chronic nephrosis or amyloidosis apart from exceptional instances of amyloid contracted kidney with hypertension. Retinal lesions have been described in rare cases of mechanical urinary obstruction (Nettleship,[9] Leber[10]). The hypertension of chronic pyelonephritis may lead to retinal lesions, as may that of periarteritis nodosa. Hypertensive retinopathy may occur in acute lead poisoning without any evidence of renal disease (Oliver,[11] deSchweinitz[12]) as well as in chronic renal disease of plumbic etiology. Oppenheimer and the writer[13] observed hypertensive retinopathy in a patient with hypertension due to a tumor of the suprarenal cortex but practically no changes in the kidney, and many similar cases have since been described Retinopathy may also accompany the hypertension of pheochromocytoma (Rodin[19]).

The classical picture of hypertensive retinopathy is most commonly seen in the malignant phase of essential hypertension, glomerulonephritis and the hypertensive toxemia of pregnancy. Most larger statistics of the in- ... value ... either ... l, that retinal lesions are present in from 20 to 35 per cent of patients dying with contracted kidneys. Thus, Miley[14] found retinal changes in 32.6 per cent of 156 such cases, Widal and Weill[15] in 32 per cent of 166 cases, and Groenouw[16] in 22.4 per cent of 935 cases of Bright's disease reported by various authors, the large majority of which were chronic forms, *i. e.*, chronic glomerulonephritis and essential hypertension Fishberg and Oppenheimer[17] observed hypertensive retinopathy in 17 of 55 cases of chronic glomerulonephritis and in 37 of 189 cases of essential hypertension. The material studied by the last-named authors consisted in hospital patients; in private or dispensary practice, the incidence of retinal lesions is not nearly so high. However, these statements hold for patients seen only for a short period; by following patients with chronic glomerulonephritis for periods up to fourteen years, Cannady and O'Hare[18] were able

A most prominent feature in most cases is the appearance in the retina of white spots, composed of areas of fatty change and edema. They are usually confined to the portion of the retina within 3 or 4 disk diameters from the papilla. At the start they frequently present an appearance characterized by the terms "cotton-wool" or "snow-bank" areas. Later, ... and more sharply outlined, bright

... apparently largely due to absorption of ... defined "hard" spots are present from the onset. The white areas are often rounded but may be irregular in outline and are occasionally surrounded by hemorrhage; they vary from tiny to very large in size. The fatty degeneration usually occurs deep in the retina, so that the larger vessels pass over it, but the reverse is exceptionally true. Most often, the white areas are in the proximity of the larger vessels. The large white areas may become confl... ...other and by joining with the white zone around the pa... central portion of ... several disk diameters from the papilla.

The larger white lesions usually spare the macula In this region there ... usually in a linear arrangement ... stellate

The stellate figure also is seen in some cases of arteriosclerotic retinopathy, ...

located

Hemorrhages are commonly present from an early stage, at times, they ... Often they are flame- ..., the long diameter ... and close to a large vessel Sometimes the hemorrhages seem to be into the perivascular sheath. Rounded or irregular hemorrhagic spots are more common peripherally. In the later stages the hemorrhages usually diminish in number, the picture being dominated by the white spots Not very rarely, no hemorrhages at all are to be seen Great predominance of hemorrhages in one eye should raise the suspicion of closure of a central vessel

In cases of long standing, pigmented areas arising from proliferation of the pigment epithelium may be seen, particularly in the periphery But they are generally not nearly as prominent ophthalmoscopically as anatomically

The Vessels – The arterial blood columns are narrowed, often to a very great extent Sometimes the constriction is so marked that there appear to be fewer arteries present than the normal number, and they cannot be followed the usual distance out from the disk The reflex stripe of the narrowed arteries is often very bright, resulting in the appearance termed "silver-wire arteries" by Gunn[26] As mentioned above, Gowers[5] observed

most often reddened, although the hyperemia is rarely of high degree. The swelling of the nerve head is largely due to edema, in addition to venous hyperemia, giving it a cloudy ap

be impossible to make out the delimitation of the papilla from the surrounding retina In other exceptional cases, on the contrary, the swelling of the disk causes it to rise abruptly from the retina so that the appearance is very similar to that of choked disk resulting from tumor of the brain. Keith, Wagener and Kernohan[21] have observed swelling of the disk of as much as 6 diopters in the malignant phase of essential hypertension and 3 or 4 diopters is not very rare. In most instances, the absence of abrupt transition resulting from the peripapillary edema makes the estimation of the elvation of the disk difficult or impossible. With the use of the Gullstrand ophthalmoscope, Larsson[22] demonstrated elevation of the disk in all his cases of hypertensive retinopathy.

As a rule the disk is not only swollen but also more or less reddened. The reddening is evidently dependent on venous hyperemia, for the veins are usually dilated and the arteries narrow. The color of the disk is greatly influenced by the hemoglobin content of the blood; if the patient is markedly anemic, which is more often the case in chronic glomerulonephritis than in the malignant phase of essential hypertension, the disk may be very pale. Very often both the hyperemia and the swelling of the disk diminish in the course of a long-standing process. In glomerulonephritis papilledema may improve greatly, or in rare instances disappear entirely, while the retinal changes remain or even progress; in such cases there may be more or less atrophy of the nerve head.

Choked Disk Associated with Edema of the Brain —In some instances of glomerulonephritis, the hypertensive toxemia of pregnancy, and the malignant phase of essential hypertension, edema of the brain leads to very marked increase in intracranial pressure (cerebrospinal fluid pressure over 400 mm of water) The heightened intracranial pressure is associated with swelling of the disk appearing like the choked disk of brain tumor Most often the papilledema is accompanied by other evidences of hypertensive retinopathy. But exceptionally, especially in acute glomerulonephritis in children, the choked disk is not associated with retinal changes. In these rare cases it seems likely that the papilledema results from the increased intracranial tension, and it has been observed to clear up after decompression.

The Retina.—The papilledema may be present for a considerable time before changes in the retina appear. In other cases, retinal lesions appear very early and may precede the papilledema.

At an early stage there often appears a grayish clouding of the retina, best marked close to the papilla and diminishing toward the periphery. This is largely du

of the nerve fibers

retina around the

by confluence with the white spots in the retina about to be described, there may arise a dense white area completely surrounding the disk.

long ago that narrowing of the arteries is the first change in the eye-ground in hypertensive retinopathy. But there may be marked narrowing of the retinal arteries in hypertensive patients for many years without any retinal lesions developing.

When hypertensive retinopathy develops in an individual who has had [illegible] for a considerable period, evidence of retinal arteriosclerosis [illegible]

[illegible] The veins are generally dilated, which, in combination with the narrowed arteries, results in an abnormally great disproportion between the two [illegible]

[illegible] in the composite ophthalmoscopic picture. Thus, in some cases, papilledema is the only change in the fundus apart from narrowed arteries; in [illegible] white areas of degeneration and edema may overwhelmingly predominate.

As a result of their extensive studies, Keith, Wagener and Kernohan[23] believe that they can often differentiate the ophthalmoscopic picture of hypertensive retinopathy in the malignant phase of essential hypertension [illegible] papillary snow-bank exudates. Edematous detachment of the retina was seen in only one case in the present series. The hyperemia of the disk is in marked contrast to the anemia of the disk and the retina that is seen in the retinitis of nephritis. Sclerosis of the retinal arterioles is always present in malignant hypertension and is usually absent in chronic nephritis." However, while these associations hold in most cases, there are also many instances in which such ophthalmoscopic differentiation between the malignant phase of essential hypertension and glomerulonephritis is impossible. It is to be remembered that in chronic glomerulonephritis of many years' duration sclerosis of the retinal arteries may be very marked, while on the other hand sclerosis of the retinal arteries may not be recognizable with the ophthalmoscope in the malignant phase of essential hypertension in very young subjects. The color of the disk and retina is greatly influenced by the hemoglobin content of the blood, which would appear to be one reason why these structures are generally more pale in glomerulonephritis than in essential hypertension.

Hypertensive retinopathy appears to be of the same pathogenesis (see below) in both essential hypertension and glomerulonephritis, the differences in ophthalmoscopic appearance, if present, being largely the result of the concomitant operation of other factors.

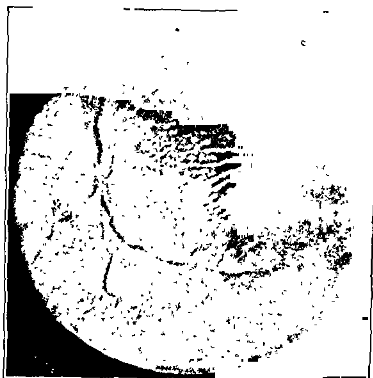


Fig 6.—Hypertensive retinopathy in chronic glomerulonephritis (Courtesy of the late Dr. Robert K Lambert. The double white disk temporal to the papilla in the photograph is an artefact)

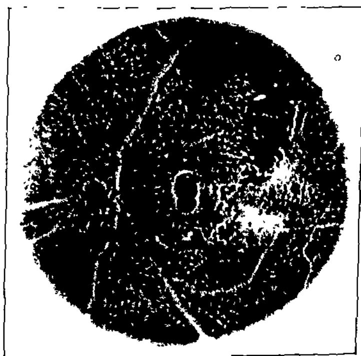


Fig 7.—Hypertensive retinopathy in the malignant phase of essential hypertension (Courtesy of the late Dr Robert K Lambert)

. . . . in the eye-ground

. . . sions developing.

When hypertensive retinopathy develops in an individual who has had hypertension for a consi . . . evidence of retinal arteriosclerosis is usually also present. . . . the retina may be comb . . . The veins are generall . . . arteries, results in an . . .

. . . lesions vary in prominence in different instances . . . in the composite ophthalmoscopic picture. Thus, in some cases, papilledema is the only change in the fundus apart from narrowed arteries; in fact, Moore[27] observed a patient in whom the papilledema was unilateral. I have repeatedly observed the papilledema to be unilateral for weeks. In other instances the papilledema is but slight for a considerable period . . . hemorrhages or

. . .

As a result of their extensive . . . that they can often differentiate the ophthalmoscopic picture of

. . .

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Pathological Anatomy of Hypertensive Retinopathy.—The anatomical basis of hypertensive retinopathy was exhaustively studied by Leber,[10] [illegible] . More recent anatomical [illegible] , Wagener and Kernohan,[28] [illegible] and Manlove.

The retinal changes are almost altogether confined to a zone of from 5 to 6 mm. from the papilla, being absent or slight beyond this. In acute cases there is usually edematous transudation into the papilla and the neighboring retinal tissue. This may be so copious as to produce large spaces filled with fluid between the tissue elements. The form of the hemorrhages has been described above; the radially elongated ones are situated in the nerve fiber layer. The extravasation is, according to Leber, largely by diapedesis.

The white spots ("exudates") are for the most part made up of large cells laden with fat and lipoid, so-called fat-granular cells. They contain particularly large amounts of cholesterol esters, exhibiting double refraction through the polarizing microscope. Swelling and necrosis of these cells leads to the formation of the so-called "cytoid bodies," which are often prominent in the sections. In the early phases, edema may be prominent between the retinal elements. Another factor in the formation of the more superficial white spots is a ganglioform swelling of the nerve fibers Fatty changes also occur in the glia fibers The origin of the fat-granular cells is disputed; Leber believes that they are derived from the pigment epithelium, others from glia cells, and the opinion has also been advanced that they are leukocytes. It seems certain that they take up the fat locally, but from what elements this comes is unknown. It is surprising how well the retinal elements may be preserved for a long time in the midst of fatty areas, but ultimately there is great destruction of the granular layers, the rods and cones, and other elements. According to Friedenwald, the great majority of the lesions which have the ophthalmoscopic appearance of "cotton wool exudates" have gone on to the stage of focal necrosis. When the white spots disappear, which they often do, Leber believes this occurs largely through removal of the fat-granular and necrotic cells *via* the blood vessels.

Leukocytic and lymphocytic infiltration is almost always minimal or absent, when white blood cells are present, they are largely perivascular The pigment epithelium proliferates in some places and disappears in others.

The arterioles show lesions in at least the large majority of instances These arteriolar changes are of various types—hyalinization, fatty changes, necrosis, endothelial proliferation, and muscular hypertrophy and other alterations in the media They have been studied in detail by Friedenwald,[29] to whose work the reader is referred. According to this investigator the primary change is an acute necrosis of the vessel wall, the outcome of which may be hyalinization and lipoidosis. Friedenwald found that the lesion is located primarily in the precapillary arterioles, but also often affects the capillaries and sometimes the larger vessels. In Manlove's[30]

[illegible]

seen frequently and necrosis rarely. These changes were more pronounced

. . the retina By measuring the wall: lumen ratio, he retinal arterioles in .eriolar changes varies

ever, ... iolar lesions were minimal or absent. ... malignant hypertension with numerous exudates and hemorrhages in which there was no arteriolar disease except a little medial thickening. In hypertensive retinopathy in the malignant phase of essential hypertension, Keith, Wagener and Kernohan found the obstruction greater in the arterioles of the choroid than in those of the retina.

Lesions in the choroid are almost always to be found in the form of leukocytic infiltrations, edematous transudates and arteriolar thickening.

The Pathogenesis of Hypertensive Retinopathy.—From the first des- ... retinal lesions in renal disease, their origin has been ascribed to ...

... retention; a series of such cases was published by Wagener and ... and they are to be seen frequently on an active medical service Not very rarely, hypertensive disease runs a protracted course with severe retinal changes, to terminate finally in death without there having been at any time nitrogen retention On the other hand, many patients die of uremia with great nitrogen retention, but no retinal lesions From these facts it seems clear that renal excretory insufficiency is not the essential cause of hypertensive retinopathy

Because of the presence of large quantities of cholesterol esters in the white spots of hypertensive retinopathy and the frequency of hypercho- ...

... form of renal disease in which hypercholesteremia is most marked, chronic nephrosis, the retinal lesions do not occur On the other hand, in the end stages of chronic glomerulonephritis and essential hypertension, in which the retinal changes are most common, the cholesterol content of the blood is rarely notably elevated, and is, in fact, often subnormal if nitrogen retention is present When present, however, increased lipid content of the plasma may well secondarily favor the deposition of lipids in the retinal lesions

many instances of hypertensive retinopathy, in others the vessels present

children, that sclerotic changes could develop in so short a time. Arteriosclerosis does, of course, produce retinal lesions, but these differ from the manifestations of hypertensive retinopathy and will be described in the next section. But that *acute* arteriolar lesions, not included in the conventional conception of arteriosclerosis, may play a part in producing the retinal lesions, will be seen below.

The one fact fundamental to any adequate consideration of the pathogenesis of hypertensive retinopathy is that it always occurs in association with *arterial hypertension*, as was long ago realized by Traube[36] on the basis of palpation of the pulse and observation of cardiac hypertrophy, and more recently emphasized and elaborated by Volhard.[37] In almost every patient with hypertensive retinopathy the blood pressure is high; in the few in whom this is not the case, the pressure has dropped because of cardiac weakness or the process is regressing. Moreover, the hypertension precedes the retinal changes. In glomerulonephritis retinal changes develop only after the blood pressure has risen, and the retinal lesions heal if the hypertension disappears. Likewise, in the toxemia of pregnancy retinopathy develops only in the wake of hypertension and clears up when the blood pressure falls. In essential hypertension the retinal lesions under discussion appear only in those cases with very high blood pressure. If low sodium diet, the use of hypotensive drugs, sympathectomy or ablation of a suprarenal tumor removes hypertension, the retinal lesions clear up. Clinical evidence thus leaves no doubt that the retinal lesions are consequences of hypertension or of the processes which produce hypertension.

That hypertension can produce retinal lesions was shown by Keyes and Goldblatt[38] in dogs and monkeys with constricted renal arteries Similar observations were made by Fasciolo and Cramer[39] and Laughlin *et al.*[40] When chronic hypertension lasting years was produced by clamping of moderate degree, there developed tortuosity, increased light reflex and white sheathing of the arterial blood columns. Hemorrhages, cotton wool exudates, edema of the retina and papilledema developed in the more pronounced cases. Like the retinal lesions of human hypertension, this retinopathy was not due to renal insufficiency for it appeared in the absence of nitrogen retention. Histologically, the retinal arterioles revealed hyalinization, endothelial hyperplasia and medial hypertrophy. When the clamp was tightened enough to produce malignant hypertension with very high blood pressure and widespread arteriolar necrosis, the retinal arterioles also became necrotic The fundus then was the seat of lesions more severe than those seen in human hypertension—extensive hemorrhages, retinal and subretinal edema, detachment—and there was bleeding into the anterior and posterior chambers of the eye.

The question then arises of the mechanism through which hypertension produces the retinal lesions It would seem that four factors may be involved:

1. Constriction of the retinal arterioles.
2. Increased capillary pressure in the retina.

3. Lesions of the retinal arterioles.

intracranial pressure

that produces the hypertension.

In hypertensive retinopathy, as mentioned above, the retinal arteries are narrowed, often to an extreme degree. Gowers[3] knew long ago that the narrowing of the retinal arteries may be present at a very early stage. I have observed marked narrowing of the arteries of the retina in acute

occasionally observed in cases in which the retinal circulation has been hampered by increased intracranial tension in brain tumor. Furthermore, the typical stellate figure around the macula has been noted in various forms of anemia, with regression after the hemoglobin has risen. (de-Schweinitz,[11] Augsten[12]). That spasms of the retinal arteries have been actually observed during hypertensive paroxysms was mentioned on page 352

Very important suppor ... tic theory of hypertensive ... of Haselhorst and Mylius[13] ... of the retinal arteries in a woman with eclampsia gravidarum. At the first examination, they found the eye-ground completely normal except for cramp-like co

The location

see the previously narrowed ...

the spasm relaxed By two days later the spasms had become more constant and involved longer stretches of the arteries At this time the first changes in the retina appeared, "which consisted at first of circumscribed, indistinctly limited, transparent, glassy, whitish-yellow lesions, appearing initially midway between the larger arterial branches Soon, however, they were visible scattered irregularly over the entire posterior pole. Besides these, there also arose a fairly diffuse edema of the macular region." Vision became so badly impaired that at times fingers could not be distinguished Cæsarian section was performed and the patient rapidly improved The vessels gradually filled, vision returned, and the retinal changes regressed, though six months later some cholesterol crystals were still present in the macula Haselhorst and Mylius photographed each stage of the retinal process and reproduced a number of convincing photographs

2 *Increase in Retinal Capillary Pressure* —In the foregoing it has been seen that there is strong evidence that angiospastic ischemia of the retina is concerned in the pathogenesis of hypertensive retinopathy It seems probable, however, that the reverse process, increase in retinal capillary pressure, may also be concerned This conception was suggested by the

observation that in many patients who had undergone thoracolumbar sympathectomy for essential hypertension, *papilledema, hemorrhages and exudates cleared up pari passu with fall in arterial pressure despite persistence of constriction of the retinal arteries, as evinced by attenuated arterial blood columns.* Such clearing of retinopathy in the presence of lower arterial pressure and persistent retinal arterial constriction does not harmonize with an ischemic pathogenesis of the lesions, but points rather to causation of the latter by increased capillary pressure. That capillary hypertension could produce hemorrhages and edema is evident. And the underlying basis of many so-called exudates is transudation of plasma, from which fluid is then abstracted, leaving lipo-protein deposits.

A working hypothesis of the pathogenesis and rôle of increased capillary pressure in hypertensive retinopathy is the following: In the case of the brain it has been proved (p. 302) by the finding of normal cerebral blood flow that the rise in arterial pressure is accompanied by commensurate increase in cerebral vascular resistance due to constriction of the cerebral arterioles. While retinal blood flow has not been measured, the narrowing of the arterial blood columns indicates that the retinal arteries are similarly constricted in hypertension. But like the cerebral arterioles, the retinal arterioles have only a thin muscular coat* and therefore doubtless share with the cerebral arterioles a much less powerful vasoconstricting ability than the arterioles of the extremities (p. 354). When the arterial pressure rises sufficiently, the arterioles of the retina may not be able to constrict with sufficient strength to maintain the homeostasis of the retinal circulation. The consequence would be rise in hydrostatic pressure in the retinal capillaries with resultant edema (papilledema, exudates) and hemorrhages. This hypothesis attributes to hypertensive retinopathy a pathogenesis akin to that of cerebral edema in hypertensive encephalopathy. But that it is no more than a working hypothesis is to be reiterated.

3. *Lesions of the Retinal Arterioles.*—It was mentioned above that necrotizing and other acutely developing regressive arteriolar lesions occur in some percentage of instances of hypertensive retinopathy. Friedenwald[29] found that these arteriolar lesions "are definitely related to the focal lesions, hemorrhages and so-called exudates, characteristic of albuminuric retinitis." Acute damage to the arteriolar walls (we are not here considering gradually-developing arteriolar sclerosis), when it occurs, is thus one of the intermediaries through which hypertension produces retinal changes. But the arteriolar necrosis and marked initimal proliferation in question are present in only some of the cases and are probably only a minor factor in at least most of the others In malignant hypertension, Manlove[30] was unable to demonstrate that arteriolar changes result in other retinal lesions and observed cases with many hemorrhages and exudates in the absence of arteriolar disease.

* [illegible]
in re [illegible]
the [illegible]
in the eye are thinner than those in other organs

4. *Increased Intracranial Pressure.*—In recent years it has become clear that increased intracranial pressure due to edema of the brain plays an important rôle in the pathogenesis of a high proportion of instances of ...tinopathy. This was long ago stated by Cushing and ... lesions following

Similar

Larsson[24]

observations have been made by ... found the pressure of the cerebrospinal fluid elevated in hypertensive patients with papilledema. Shelburne, Blain and O'Hare[46] observed that 19 of 20 hypertensive patients with a cerebrospinal fluid pressure of over 200 mm. of water had papilledema, while the latter was present in only 2 of 30 with lower tension of the liquor. Pickering[47] found hypertensive retinopathy in all his hypertensive patients with cerebrospinal fluid pressure ... of water, this lesion was present in only 1 of 21 patients ... the ... mit-

... was well marked and often ...

no edema of the disk even though the retinal lesions were ... Well marked papilledema in hypertensive retinopathy is evidently correlated with increased intracranial pressure. The same is true of pronounced distention of the retinal veins, which often precedes manifest edema of the disk.

It would thus appear that hypertensive retinopathy is a consequence of circulatory disturbances in the retina. The homeostasis of the retinal circulation demands that the arteriolar resistance, *i. e.*, the caliber of the arterioles, be altered commensurate with the rise in systemic arterial

circulatory disturbances through the intermediacy of four mechanisms—constriction of the retinal arterioles, increase in retinal capillary pressure, lesions of the walls of the retinal arterioles, and increased intracranial pressure. The relative importance of these factors varies in different instances of hypertensive retinopathy, and thereby accounts in large part for the diversity of the ophthalmoscopic pictures. Where papilledema and venous distention are pronounced, increased intracranial pressure is

under observation, speaks for constriction. Clearing of the lesions when the arterial tension falls (*e. g.*, after sympathectomy) despite persistence of the arterial narrowing speaks for the operation of raised retinal capillary pressure. Regarding the ophthalmoscopic manifestations of the acute arteriolar lesions here under discussion (we are not considering long-standing arteriolar sclerosis), little is known. According to Wilmer,

Pierce and Friedenwald,[48] hyaline thickening and necrosis are manifested by a copper wire appearance of the vessels. That accompaniment of the causative hypertension by hypoproteinemia or hypercholesterolemia would influence the form of the retinal lesions seems plausible.

The Symptoms of Hypertensive Retinopathy.—In rare instances, impairment of vision due to hypertensive retinopathy is the first symptom of hypertensive disease, the patient going to an ophthalmologist in the belief he needs glasses. Such cases occur particularly in the malignant phase of essential hypertension. More often, patients with very extensive changes in the retina make no complaint about disturbances of vision; this is because the macula is relatively unaffected. In other cases, there are varying degrees of impairment of vision, attaining in unusual instances a high degree of amblyopia. Complete blindness as a result of hypertensive retinopathy is extremely rare; it may be due to hypertensive encephalopathy, which may be proved by complete recovery of vision within a short time without any improvement in the objective retinal findings. There is usually no considerable narrowing of the visual fields. Color scotomata, particularly circumscribed areas of blue blindness, have been reported in many cases.

Complications of Hypertensive Retinopathy.—Of these, the most important is detachment of the retina; in 204 cases collected from the literature by Leber, it occurred in 2.9 per cent. Detachment of the retina is decidedly less rare in hypertensive retinopathy during pregnancy than in other cases. It is usually bilateral. The prognostic significance of detachment of the retina is very bad in all cases except those occurring during pregnancy, the duration of life being short (Leber[10]). If termination of pregnancy halts the basic disease, the retina re-attaches with healing. The same occurs in very rare cases apart from those during pregnancy, Moore[27] mentions one such case in which the man lived for seven years after the detachment, and I saw a young woman with chronic glomerulonephritis who was alive a year and a half after detachment of the retina resulting [illegible] branches, secondary glaucoma, and hemorrhage into various portions of the eyeball These are probably almost always due to concomitant arteriosclerosis. Another rare complication is sudden blindness, due to hypertensive encephalopathy.

Prognostic Significance of Hypertensive Retinopathy.—The appearance of hypertensive retinopathy has long passed, and rightly so, as a very ominous prognostic sign. This is particularly the case in chronic glomerulonephritis and essential hypertension, in which the appearance of hypertensive retinopathy is one of the strongest evidences that the disease has entered on its last phase. Numerous statistics have shown that about 90 per cent of patients with hypertensive retinopathy die within two years Most of the few that survive the first two years die within the next year or two. Individual cases have been recorded that survived long periods; Leber[10] mentions one that is said to have lasted seventeen years. I observed a hypertensive patient who had typical hypertensive retinopathy that cleared up after about a year; despite persistence of his hypertension he

was able to work for nine years. His condition then became worse and the retinal lesions reappeared. *Necropsy* disclosed the typical findings of the malignant phase of essential hypertension. Keith and Wagener[49] report 15 cases in which the papilledema of *malignant* hypertension receded

... of cortical or medullary ... has been

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retinopathy ...

bad as in chronic states, and some patients recover despite the presence ... marked retinal changes. Indeed, if one examines the eye-grounds repeatedly, retinal changes of slight degree, notably one or a few hemor- ... many cases that have a mild course. Well-

disease in pregnancy and eclampsia gravidarum generally hangs together with that of the hypertension and renal process. If termination of pregnancy is followed by healing of the kidneys, and fall in blood pressure, the retinal process will also regress The healing of the retinal lesions may be complete or a permanent defect of vision may remain. This may be slight or severe, in unusual instances, almost complete blindness results Detachment of the retina is usually completely repaired if the patient survives The appearance of hypertensive retinopathy during pregnancy is evidence of a severe and rapidly progressive process, and is an indication for termination of pregnancy Almost all toxemic patients with hypertensive retinopathy remain with permanent hypertension (*cf.* p 962).

Spontaneous Healing —When hypertensive retinopathy is followed over a considerable time,

of individual "exudates"

are usually observed As ...

fresh lesions that appear But if the fundamental disease, acute glomerulonephritis or hypertensive disease in pregnancy, regresses, accompanying hypertensive retinopathy will also clear up Under such circumstances, very severe retinal processes may disappear completely, though this is, of

... he stellate figure around the macula,

... spots is usually the last to clear up.

... mal, or more often, if the process has been well marked, changes are left The disk is atrophic, appearing white and very sharply delimited The arteries may be *narrowed with white* lines accompanying them Holm[52] and others have described *cases in which* there was extensive circumpapillary formation of connective tissue with jagged outlines as an indication of *shrinkage.*

There may, on
retina which is th
of glomerulonephritis or hypertensive disease in pregnancy. Such a case was observed in a boy, aged thirteen years, who remained amaurotic in one eye following the healing of retinal lesions accompanying acute glomerulonephritis four years previously. Both eyes showed evidences of optic atrophy, the arteries were much narrowed with white streaks on either side, and in the macular region of the amaurotic left eye there was a dense, old, white area. The recent changes consisted in hemorrhages and white spots, but there was no notable change in the atrophic papillæ. These fresh lesions cleared up, leaving the retina as it had been before the second exacerbation.

II. ARTERIOSCLEROTIC RETINOPATHY

While it has long been known that arteriosclerosis can produce retinal lesions, the more severe retinal manifestations of arteriosclerosis are included in the old literature under the concept of "albuminuric retinitis." So far as I am aware, Foster Moore[53] was the first to give an adequate description of the variegated retinal pictures resulting from arteriosclerosis and to differentiate them from what he termed renal retinitis. He called the condition arteriosclerotic retinitis, but inasmuch as the process is clearly not inflammatory in nature, we shall use the term arteriosclerotic retinopathy.

Retinal arteriosclerosis occurs in individuals who have had high blood pressure for a considerable period, usually many years. O'Hare and Walker[54] pointed out that widespread arteriosclerosis of the large vessels in the absence of hypertension is most often not accompanied by notable changes in the retinal arteries. However, there are exceptional cases in which retinal arteriosclerosis and arteriosclerotic retinopathy develop in the absence of hypertension. As would be expected from its connection with long-standing hypertension, retinal arteriosclerosis is seen most frequently in essential hypertension (p. 813) but is not rare in chronic glomerulonephritis. I have also seen retinal arteriosclerosis in hypertension resulting from amyloid contracted kidneys and from polycystic disease of the kidneys. Diabetic retinopathy may or may not be accompanied by ophthalmoscopically demonstrable arteriosclerosis. Judging by the description given by Duckworth,[55] "gouty retinitis," which I have not seen, may be a form of arteriosclerotic retinopathy.

Signs of Retinal Arteriosclerosis.—The ophthalmoscopic manifestations of retinal arteriosclerosis vary considerably in individual cases, for which reason there has not been complete accord as to the relative value of the individual signs. Still not elucidated in all respects is the differentiation of hypertonicity of the retinal arterioles and thickening of their walls. Among the more valuable signs are the following:

1. Irregularity of outline of the arterial blood columns resulting from persistent circumscribed constrictions and dilatations of the lumen of the artery is evidence of well-marked arteriosclerosis. It is a common sign but is not definitely demonstrable in all cases. Irregularity of the arterial

lumens is generally observed only in long-standing arterial disease, but Moore[27] saw it develop to a high degree within eighteen months in a case of war nephritis. Leatham[6] observed irregularity of the borders of the arterial blood columns in 76 per cent of his hypertensives. So high a percen ... dy by careful examination of all the arteries out tc ... refract... Transient irregularities due to spasm are mentioned above, ... is rare. Definite irregularity of the arterial lumen hardly occurs in the absence of arterial disease.

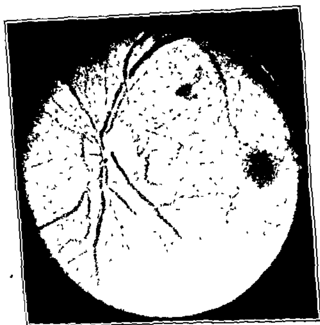


FIG 8 —Retinal arteriosclerosis in essential hypertension; note the arterio-venous compression above (Courtesy of the late Dr. Robert K Lambert)

Uniform narrowing of the arterial blood columns is not in itself evidence of arteriosclerosis, it may appear with the hypertension of the toxemia of ... been time for the ... ig is presumably a ... n the aged, narrow ... of any evidence of hypertension past or present Whether this attenuation bespeaks uniform thickening of the arterial wall remains to be established

2 Visibility of the arterial walls is evidence that they are diseased in ... s ... a striking manifestation of retinal arteriosclerosis, but it is absent in many

instances. When the vessels are healthy, the retinal veins are visible until they reach the arterial blood column under which they pass and often through it. If arterio-venous compression is present, the vein becomes invisible or appears attentuated for a short distance from the edge of the arterial blood column under which it passes. Shelburne[57] points out that crossings within one disc diameter of the papilla should not be used for evaluation of nicking for here the latter may be simulated by the vein dipping deep into the retina. In a good many instances, one can observe that the flow of blood in the vein is actually impeded, for the venous blood column is wider and darker before reaching the artery than after. Another feature pointed out by Moore is that the vein often bends so as to pass under the vein at approximately [illegible] distance from the arterial blood column is due to opacity of the sclerosed and thickened arterial wall under which the vein passes. Another factor that probably also plays a part has been brought out by Friedenwald,[29] who has demonstrated that artery and vein are enclosed in a common connective-tissue sheath at the point of crossing, which is greatly thickened when arteriosclerosis is present. The thickening of the arterial wall and the common connective-tissue sheath causes the appearance of arterio-venous compression not only through their opacity but, very likely, also through displacing the vein [illegible] and the two ends of the vein, occurs only with present or past hypertension of marked degree. The finding of pronounced arterio-venous compression in a normotensive individual thus permits the inference of antecedent marked hypertension. In Shelburne's observations it took years of marked hypertension for the evolution of a high degree of arterio-venous nicking.

4 Increased tortuosity of the arteries is a frequent manifestation of arteriosclerosis However, healthy vessels may also be quite tortuous, so this sign must be evaluated with caution unless it is very marked. Of particular significance, though rare, is a "cork-screw" appearance of the small vessels in the region of the macula. Friedenwald and Friedenwald[58] point out that at times these are the only vessels in the retina to show definite changes, which is perhaps correlated with the fact that they are the smallest arterial vessels that can be seen ophthalmoscopically (internal diameter 10 to 15 microns, according to Friedenwald and Friedenwald).

5. Changes in the color of the arteries and in the brightness and width of the reflex stripe have been attributed significance for the diagnosis of retinal arteriosclerosis. Appearances characterized as "copper-colored" and "silver-wire" arteries are not uncommonly seen as a result of changes in the walls. Increased brilliancy and broadening of the reflex stripe are sometimes considered as evidences of retinal arteriosclerosis but normal variations in these respects are so great that the Friedenwalds consider the findings of no clinical significance. Irregularity of the reflex is of more importance for the recognition of arteriosclerosis.

... in Arteriosclerotic Retinopathy.—Retinal ar- ... without producing ... In other cases, ... retina, which may ... however, the vascular lesions ... ristic and striking. ... importance for the dif- ...

... be some haziness of the margins of the ... rare cases of long duration, arteriosclerotic atrophy develops



Fig. 9 — Arteriosclerotic retinopathy in essential hypertension. The papilla is unaffected. There is a venous closure above. (Courtesy of the late Dr. Robert K. Lambert.)

In the retina, hemorrhages constitute the most common finding, they may be few or many in number, superficial or deep, rounded, linear or irregular in shape. The hemorrhages are often accompanied by white spots, especially the cases in which the latter are prominent were formerly confused with hypertensive retinopathy. But while in hypertensive retinopathy the "exudates" may have either the soft appearance described as cotton-wool or be "hard" and sharply delimited, in arteriosclerotic retinopathy the white areas are "hard," sharply delimited and often shiny, edema evidently plays little part in their production. The color varies from dead white to yellowish. The white spots vary greatly in number, most often there are none or few, but in exceptional instances they are very numerous. As a rule the individual areas of degeneration are small,

but there may be a few large lesions. In some instances the spots have an irregularly stellate or circinate arrangement in the macular region. Choroidal sclerosis with pigment changes is often to be seen.

Although retinal arteriosclerosis is bilateral, the resulting changes in the retina are not uncommonly unilateral for a long period, as was true in 45 per cent of Moore's cases. In consequence of formation of new lesions and disappearance of old ones, especially hemorrhages but occasionally also white spots, the picture may vary greatly from time to time.

The effect on vision is, of course, dependent on the location of the lesions and the occurrence of complications. Among the latter are thrombosis of a central vessel, optic atrophy, glaucoma and, what is extremely rare, transitory blindness due to arterial spasm. It need scarcely be added that hypertensive retinopathy not uncommonly develops in a retina already the seat of arteriosclerotic changes.

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Chapter 13

THE SUBDIVISION OF BRIGHT'S DISEASE

Before Bright.—Every discoverer has his precursors, and Bright was no exception. It was pointed out in Chapter 6 that the association of diseased kidneys with dropsy had been noted by isolated observers, beginning with ancient times. These individual observations, however, influenced neither the practice nor the theory of medicine. The first real step in the study of the pathological states later described by Bright was the discovery by Cotugno[1] that the urine of dropsical patients is albuminous. Cotugno arrived at this important finding in the following curious manner: He had observed that the fluid of dropsical effusions is coagulable by heat. Cotugno had further noted that the absorption of such effusions is accompanied by increased urinary output and, therefore, believed that the dropsical fluid is eliminated through the urinary passages. To test this theory, he investigated if the urine of such patients has the same property of coagulation by heat as the effusion, and found that such is actually the case.

Toward the end of the same century, Cruikshank[2] found that albumin is not present in the urine of all dropsical patients. He stated that coagulable urine occurs only in individuals with "general dropsy," while the urine is free of albumin in those whose dropsy depends on unsound viscera, *e. g.*, disease of the liver. Blackall[3] arrived at similar conclusions. About the same time, Wells[4] carried out important studies on the urine of patients with scarlet fever. He found that the urine in postscarlatinal dropsy is often bloody. In other such edematous patients, though the urine was free of blood corpuscles, it was coagulated by heat, so that he believed that it contained blood serum. Both Wells and Blackall observed lesions of the kidneys in some patients with dropsy and albuminous urine, but in other cases they did not find these renal changes and were, therefore, unable to decide whether the albuminuria and dropsy were actually results of renal disease. During the same period, Darwin,[5] Brande,[6] and others studied albuminous urine, but the investigations just cited represent the most significant work of the time in this field, and undoubtedly laid the foundations for the epoch-making investigations of Bright.

The Work of Bright.—In 1827 Richard Bright,[7]* lecturer on the Practice of Medicine at Guy's Hospital, published the first volume of his *Reports of*

* For an appreciation of the personality of Bright, as well as of his work, which is and presumably always will remain
stones of all clinical medicine,
Thayer[8] on the occasion of th
Cases. Dr. Osman[9] has perfo[illegible]
Bright's original papers on renal disease.

ases Illustrative
tion of Diseases
ey." The fact of
inous urine was
the association of dropsy, diseased
demonstrated by masterly clinical descriptions of 24 such cases, in 18 of which the anatomical findings at necropsy were not only accurately de-
illustrated by a series of color plates scarcely surpassed in
to precise de-

theorizing little and speculating
few of his statements are susceptible of adverse criticism in the light of present-day knowledge He was helped by the chemical observations of
incorporated as letters in the *Reports*.

at

tical

type, Bright includes cases of glomerulonephritis
a typical example of acute glomerulonephritis.

"The third form of disease is where the kidney is quite rough and scabrous to the touch externally, and is seen to rise in numerous projections not much exceeding a large pin's head, yellow, red, and purplish" The cases he describes are instances of chronic glomerulonephritis with secondary contraction

Bright was not altogether certain whether the three groups which he described were separate diseases or different stages of the same malady, though he evidently inclined to the former opinion. Thus, he stated, "Although I hazard a conjecture as to the existence of these three different forms of disease, I am by no means confident of the correctness of this
generacy to which
all the other cases,
considered only as modifications, and more or less advanced states of one and the same disease"

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Thayer[8] on the occasion of the centenary of the publication of the *Reports of Medical Cases*. Dr Osman[9] has performed the valuable service of republishing in one volume Bright's original papers on renal disease.

causes secondary atrophy of the specific elements of the kidney. The clinical picture of chronic interstitial nephritis was dominated by cardiovascular phenomena, *notably increased arterial* tension, arteriosclerosis, and cardiac hypertrophy, with marked tendency to cerebral hemorrhage.

The untenability of the separation of chronic parenchymatous and chronic interstitial *nephritides* was demonstrated by Weigert[31] in a pri- ... al study. He pointed out that in all instances of paren-

Bright's disease into parenchymatous and interstitial nephritis became standard teaching and remained so until within recent years. It is, for instance, accepted in many editions of Osler's textbook. But at no time did this simple classification of chronic renal disease actually satisfy either clinician or pathological anatomist, and numerous attempts—the most

etiology, obviously the ideal, began to be a possibility. *Unfortunately*, the etiology of the most common form of Bright's disease, essential hypertension, has *remained* shrouded in darkness. Early in this century, the advent of "functional thinking" in organ pathology and the development of tests of renal function led to attempts to classify Bright's disease on the basis of the nature of the impairment of renal function. In France, for the first three decades of this century, the primary subdivision of nephritis

... correlation between etiology and the nature of the derangement of renal function

PRESENT-DAY NOMENCLATURE AND SUBDIVISION OF BRIGHT'S DISEASE

It has long been evident that *the term Bright's disease* ...

question that next engaged some of the best medical minds of the time and called forth an enormous literature was one ...

... stages of ... the same process.

In France, Rayer[12] maintained that Bright's disease is an inflammation of the kidney which he termed albuminous nephritis* (*néphrite albumineuse*), but differentiated six varieties of this inflammation. Frerichs,[13] one of the outstanding German clinicians of the post-Brightian period, likewise considered Bright's disease to be a single inflammation of the kidney, and recognized three stages: An initial hyperemia, a secondary period of exudation with fatty degeneration of the renal epithelium, and a third stage of connective-tissue hyperplasia terminating in atrophy of the kidney. This unitaristic interpretation of Bright's disease had many adherents for a long period.

It was, however, quickly recognized by a number of observers that Bright's disease really includes several distinct entities. The independence of the amyloid kidney and of chronic passive congestion of the organ with albuminuria and cylindruria resulting from cardiac failure was admitted, and adequate clinical criteria for their differentiation elaborated by Traube.[14] The plural nature of the other varieties of Bright's disease was also maintained by various observers, notably English clinicians. Thus, Johnson[15] differentiated a number of diseases on the basis of the state of the renal epithelia Wilks[16] also upheld strongly the view that different diseases are comprehended under the term Bright's disease. He writes that " ... me conditions—the one, a ... size, and associated with a ... dropsy of the whole body; the other, a kidney, hard and contracted, often only half the natural size, chronic in character and often destitute of symptoms." Gull and Sutton's[17] and Ziegler's[18] emphasis of the significance of the arteriolar lesions in causing the contracted kidney also helped to establish the heterogeneous nature of Bright's disease The pluralistic conception of Bright's disease was likewise strongly advocated by Grainger Stewart,[19] who entitled his monograph "Bright's Diseases."

In accord with the findings of Wilks, and especially as a result of a systematic treatise by Bartels,[20] it became customary during the third quarter of the past century to consider chronic Bright's disease as consisting of two varieties, chronic parenchymatous and chronic interstitial nephritis. Chronic parenchymatous nephritis was described as consisting in an ... ich, in accord with ... went through stages of cloudy swelling, fatty degeneration, and finally disintegration. The clinical manifestations of parenchymatous nephritis were notably renal edema, oliguria, and marked albuminuria. Chronic interstitial nephritis, on the other hand, was thought to consist in a primary proliferation of the interstitial connective tissue of the kidney, which by pressure

* So far as I am aware, this is the first use of the term nephritis to designate the diseases described by Bright.

... the complication of essential hypertension by inflammatory

...

a diversity of diseases. They have in common only ... diseased at some stage of their evolution** and that the clinical picture includes one or more of the manifestations—edema, proteinuria or hypertension (cardiac hypertrophy)—which Bright observed in his original cases. The diseases in question are so heterogeneous that at present a ... classification based on a unitary criterion does not seem feasible.

THE FORMS OF BRIGHT'S DISEASE

Orthostatic proteinuria intermittent venous hyperemia of the kidney

Nephrosis non-inflammatory lesions of the nephron
Necrotizing nephrosis
Chemical origin
...
Renal amyloidosis
Specific toxemia of pregnancy

Nephritis inflammatory lesions of the kidney
Glomerulonephritis
Focal glomerular lesions of subacute bacterial endocarditis
Wire-loop glomerular lesions of disseminated lupus erythematosus
Focal nephritis
Acute interstitial nephritis
Pyelonephritis

Essential hypertension arteriolosclerotic lesions of the kidney (at advanced stage)

These entities will be characterized in the individual chapters. Here, however, a few preliminary comments may not be amiss.

The term nephrosis has been deprecated as an etymological monstrosity meaning *full of kidney*. However, Allen[27] quotes from Webster's Inter-

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disease While this terminology has the virtue of simplicity, it will be noted that the first variety is defined on the basis of a symptom, hematuria, while the other two are

...

have been regarded by Bright as suffering from the disease described in his masterpiece, essential hypertension may terminate from cerebral hemorrhage before the microscope shows renal changes

of the clinical and anatomical characteristics described by Bright. Differentiation of these individual forms of Bright's disease resulted from many widely separated investigations. These studies will be considered in the individual chapters. Among them the following may be mentioned here as having contributed notably in the separation of the entities collectively designated as Bright's disease:

1. In 1872 Gull and Sutton[17] showed that in some types of Bright's disease the primary anatomical changes are located in the arterioles and capillaries of the kidney and other organs. They designated the process as arterio-capillary fibrosis. Later, Allbutt and Huchard (*cf* Chapter 24) showed that in at least many of these cases hypertension antedates the anatomical changes, and what is now known as essential hypertension was recognized.

2. In 1879 Langhans[23] found in an anatomical study that one variety of Bright's disease starts with inflammation of the glomeruli alone. He termed this disease glomerulonephritis. Glomerulonephritis was known from the start to be a consequence of infection, which subsequent studies showed to be almost always streptococcic.

3. In 1905 Friedrich Mueller[24] pointed out the desirability of separating the primarily degenerative from the inflammatory lesions of the kidney. He proposed that the term nephrosis be used to designate the primarily degenerative forms of renal disease

Volhard and Fahr's Pathogenetic Classification.—These differentiations were integrated into Volhard and Fahr's pathogenetic classification of Bright's disease A pathogenetic classification is based on the nature of the pathological processes occurring in the diseases under consideration. Of necessity, such a classification includes a large anatomical element, for the location of the morbid changes must also be considered. A pathogenetic classification that received wide acceptance was developed by Franz Volhard and Theodor Fahr, the one a clinician and the other a pathological anatomist, who published in 1914 a brilliant monograph[25] on Bright's disease which [illegible] knowledge of the field. They suggeste[illegible]

Volhard an[illegible] C[illegible] Bright's Disease.—A Degenerative diseases, *nephroses*, with or without amyloid degeneration of the vessels. Subvariety: Necrotizing nephroses

B Inflammatory diseases, *nephritides*

1. Focal nephritides
   (a) Focal glomerulonephritis
   (b) Septic (interstitial) focal nephritis
   (c) Embolic focal nephritis
2. Diffuse glomerulonephritis.

C. Arteriosclerotic diseases, *scleroses*.

1. Benign hypertension
2. The combination form: Sclerosis plus nephritis

It will be noted that pyelonephritis is not included in the above classification, the importance of this condition was not recognized at the time. By the combination form Volhard and Fahr meant what is now known as malignant hypertension; they believed at the time that this clinical picture

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national Dictionary that one meaning of the suffix -osis is "an abnormal or diseased condition." To the writer it seems that a generic term for the non-inflammatory lesions of the nephron is needed, and nephrosis serves this purpose adequately. The use of the word myocarditis to designate not only the rheumatic and other true myocarditides but also the clearly degenerative lesions resulting from obstruction of the coronary arteries was long a roadblock to the undertsanding of cardiac disease; and the same has been true of the use of nephritis for both inflammatory and non-inflammatory lesions of the kidney. It will be noted that nephrosis is defined as designating the non-inflammatory lesions *primarily involving the nephron* and thus does not include the regressive changes secondary to arteriolosclerosis. Further, the term non-inflammatory is used; the word degenerative, originally used by Friedrich Mueller, is not appli ... se some of the ... nd hyaline prote ... s regressive in nature but manifestations of storage.

Chronic (lipoid) nephrosis, the wire-loop lesions and focal nephritis have not been universally accepted as nosologic entities. The reasons why they are so considered in this book are given in the individual ...

... is a syndrome which may complicate any disease with diastolic hypertension, provided the latter is high enough (*cf* p. 822).

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... this book and by others, the term *benign albumin-*

...

the experience of the past fifteen years has ... other than typical orthostatic proteinuria one can not predict with certainty the subsequent course of any proteinuria in childhood. Even minimal proteinuria discovered incidentally in a school examination with little abnormality in the sediment, without history of antecedent infection, and no subjective symptoms, may prove to be a manifestation of chronic *glomerular nephritis.* For this reason the term benign proteinuria should be used only for the demonstrably orthostatic cases.

THE OCCURRENCE OF ORTHOSTATIC PROTEINURIA

Orthostatic proteinuria occurs predominantly in the second half of childhood and adolescence. While cases have been reported as early as the second year (Jehle[11]), they are rare before the sixth year, then increasing in frequency to attain a maximum at the time of puberty. An extensive investigation of the incidence of proteinuria was carried out by Lauener,[12] whose findings are summarized by Calvin, Isaacs and Meyer[13] in the following table:

		Percentage				
Age, years	*No. of children*	*Albuminuria*	*Boys with albuminuria*	*Girls with albuminuria*	*Trace of albumin*	*2+ or more*
6 to 7	1246	6 7	5 0	8 5	5 6	0 2
10 to 11	1350	27 0	18 6	35 5	15 6	5 7
15 to 16	2481	38 0	29 5	46 0	25 5	3 2

Saito[14] found proteinuria in 15 per cent of 140 healthy schoolboys and Langstein[15] in 12 per cent of children over five years of age treated in the dispensary. On the other hand, Hamill and Blackfan[16] showed that if the *urine is examined repeatedly*, the incidence of proteinuria is much higher. They found protein at one time or another in 88 7 per cent of 124 children between the ages of eighteen months and fourteen years. The acetic acid body was present in 85 4 per cent and albumin in 27.4 per cent of these urines. Orthostatic proteinuria is much less common in adults than in children, but is not rare, particularly in young adults. We have mentioned above the findings of Leube and Maclean which revealed that about 5

of proteinuria in susceptible individuals (see below). However, Diehl and McKinlay[17] found almost the same incidence of proteinuria in male students at the University of Minnesota; 5.32 per cent of 20,000 students had albumin in the urine on the examination of a single specimen with the nitric acid ring test. Of those with such a single positive test, only 11.8 per cent

Chapter

14

ORTHOSTATIC PROTEINURIA

NOT long after Bright's discovery of the relations between renal disease and proteinuria, observations were made of individuals who, despite proteinuria of many years' duration, showed no impairment of health. As early as 1841 Becquerel[1] described a man who had proteinuria but was otherwise healthy. Vogel[2] noted that such harmless proteinuria is apt to be present during the day and absent at night. In 1873 Sir William Gull[3] stated that "boys about the age of puberty frequently had albuminuria, becoming languid, weak and pallid;" he did not know the cause of the proteinuria.

The attention of the profession generally was first called to the frequency of proteinuria not due to any demonstrable organic disease in 1878 by the publications of Moxon[4] and Dukes[5] in England and Leube[6] in Germany. Moxon described the occurrence of "chronic intermittent albuminuria" in individuals, particularly adolescents, in whom there was no other evidence of renal disease Analogous observations were made by Dukes on boys at Rugby. Leube found that of 119 healthy soldiers about 4 per cent had protein in the urine passed on rising in the morning and that this incidence rose to 12 per cent after marching. The amount of protein was small in all instances, not exceeding 0.1 per cent He was unable to find evidence of renal or other disease in any of the men exhibiting proteinuria. Similar results were obtained by Maclean[7] in an extensive investigation during World War I. He found that about 5 per cent of 50,000 soldiers in training had protein in the morning urine. Exercise increased the incidence of proteinuria in one group of 200 men from 7 to 14 per cent.

Pavy[8] found that proteinuria in children and young adults without renal disease is not constant but occurs in cycles. The protein is absent in the first urine of the morning, [illegible]
diminishes, often to vanish co[illegible]
He, therefore, termed the cond[illegible]
made the important observation that the appearance of the protein is connected with the assumption of the erect posture and used the expression postural albuminuria. The importance of the change from the reclining to the erect posture is emphasized in the expression now generally used, orthostatic albuminuria, introduced by Teissier.[10] Because the urinary protein may include serum globulins as well as albumins, the term orthostatic proteinuria will be used in this book.

demonstrated in all cases. Saito[14] found 90 per cent of not demonstrably nephritic proteinuria between the ages of ten and fourteen years to be of ... hand Hamill and Blackfan did not

... accord with the results of other investigators ... experience. Calvin, Isaacs and Meyer found most of their cases not to be orthostatic Jehle ... that careful study is often necessary to demonstra... devised by him ... of change in posture ... ...ren with ...

While in some instances the proteinuria is ... ...ng present every day, in others it is highly irregular, vanishing and reappearing for ... con- ... all in- ...

... acid body ... in benign proteinuria to be but 2, a much lower ratio than is usually found in organic disease of the kidney In cases in which he brought on the proteinuria suddenly, Jehle found that serum albumin appeared in the urine ten or twenty minutes before the acetic acid body could be demonstrated

It was formerly ... but it is now know... in small numbers a...

posture sometimes contains large numbers of casts and renal epithelial cells. Calcium oxalate crystals are a common finding, as already noted by Pavy Heubner[20] states that in girls nearing puberty it is very common to find large masses of vaginal epithelium, which disappear when the proteinuria clears up

At the height of the proteinuria there is more or less marked oliguria and usually a diminution in the chloride content of the urine (Loeb[25]), the other urinary constituents being present in normal amount. These changes are those which would be expected in slight circulatory stasis. It is to be emphasized that *in orthostatic proteinuria tests of renal function performed in the usual way show no functional impairment of the kidney.* However, Rytand found in two subjects with orthostatic proteinuria that the urea and creatinin clearances in the erect posture were only one-half as great as when recumbent Bull[31] observed that during the proteinuria renal blood flow and glomerular filtration are diminished and the filtration fraction is increased. There is no nitrogen retention in the blood. The plasma proteins are also normal (Swanson and Schultz[26]). The extrarenal

showed persistent proteinuria and only 6.5 per cent had evidence of probable kidney disease. In 4500 persons aged between fourteen and seventeen years, who were examined for occupational fitness, Nowak[18] found orthostatic proteinuria in 524, *i.e.*, 11.6 per cent. King and Gronbeck[52] calculated that of 75,000 cases in the literature of the age of inductees, 3.3 per cent had proteinuria. Pavy's oldest patient with cyclic (orthostatic) albuminuria was forty-nine years of age. I have seen orthostatic proteinuria in the thirties, and once in a man of fifty with a marked spinal deformity.

As far as sex is concerned, the statistics of Lauener and of Calvin, Issacs and Meyer show benign proteinuria to be more frequent in girls than in boys, the latter authors finding protein about twice as often in the urines of girls.

An interesting observation, which accords with the great discrepancies between different statistics of the frequency of benign proteinuria has been made by Ashburn.[15] ınd that the incidence oı , at times assuming almost epidemic proportions. The cause of these fluctuations was not clear and confirmation would be desirable.

THE CLINICAL PICTURE OF ORTHOSTATIC PROTEINURIA

In many instances, the proteinuria follows the characteristic cycle mentioned above. The first urine of the morning, if passed before the patient has left bed, is free of protein. During the early morning hours protein appears, quickly reaches a maximum, and then diminishes as the patient goes about during the day. By evening it has often disappeared completely. This cyclic occurrence is, however, not an essential characteristic of the proteinuria but is due, as shown by Stirling and Heubner,[20] to the fact that the proteinuria is provoked by the assumption of the erect posture, and the ordinary habits of life involve rising in the morning. If a person with orthostatic proteinuria stays in bed all day and rises toward evening, the proteinuria will appear at that time. Heubner showed that the appearance of protein is due to the actual act of assuming the erect posture, so that the maximum amounts of protein are found if the first urine formed after rising is examined. Afterward, the quantity diminishes Jehle[21] found as high as from 0.4 to 1.2 per cent of protein in the urine formed shortly after standing, while examination of the total day's urine of the patient showed only a minimal amount of protein. Most often, the amount of protein lost in the urine is insignificant from the point of view of the organism as a whole. However, Peters and Van Slyke[22] have found as much as 3 grams of protein in the twenty-four-hour urine of apparently healthy young adults. Moving about tends to diminish the proteinuria, standing erect, as in the military position of attention, to increase it. The effect of posture on the proteinuria will be discussed further in connection with the pathogenesis.

There is no general accord as to what portion of the not demonstrably nephritic proteinurias of childhood is of the orthostatic type, *i. e.*, induced by the erect posture. Jehle believes that the influence of posture can be

coincidence. In France the view was ... proteinurias are often indicative of a tuberculous infection and the term pretuberculous albuminuria (Teissier) applied to them. As a matter of fact, however, children with orthostatic proteinuria show no special

the
ause

that

orthostatic proteinuria and the writer has ... observation

Early observers noted that many of those with benign proteinuria present what they regarded as evidence of *constitutional inferiority*, for which reason the term constitutional albuminuria was applied to the condition by Martius[31] Among 171 children with benign proteinuria, Martius found only 8 who were not in some way what he regarded as constitutionally inferior, to the writer, Martius's criteria for "constitutional inferiority" would seem to exempt few children from this designation. Speaking in favor of a constitutional factor in the pathogenesis of orthostatic proteinuria is the not rare familial occurrence, Munk[31] studied a family in which 4 of the 5 children had orthostatic proteinuria, in each instance beginning about the eighth year, and Wetherbee and Foley[32] observed orthostatic proteinuria in homologous twins However, a specific constitutional anomaly has not been established as the basis of orthostatic proteinuria After a review of the extensive older literature on the relation of constitutional types t
clusion that there is no
orthostatic proteinuria
children of asthenic habitus and this has seemed to be true in the cases which I have seen, Bull,[31] on the contrary, noted no correlation between postural proteinuria and body build Orthostatic proteinuria has been observed in association with congenital heart disease The suggestion of retarded development of the kidney (Teissier) is unsupported by cogent evidence

Lordosis.—While it has been known since Stirling's (*loc cit*) paper that in many cases of benign proteinuria, protein appears in the urine only when the patient is in the erect posture, no plausible explanation of this phenomenon was advanced until the publications of Jehle,[33] beginning in 1908. Jehle made the interesting and important observation that most of those with orthostatic proteinuria have, when in the erect posture, a well-marked lordosis, the deepest part of which is at the level of the first and second lumbar vertebræ This lordosis disappears when the patient reclines. Jehle was able to show further, by a beautiful series of observations, that

symptoms so often associated with renal disease, edema and hypertension, are always absent. Bass and Wessler[27] have found that the blood pressure of children with orthostatic proteinuria does not differ significantly from that of other children.

Most children with orthostatic proteinuria do not appear robust. They are usually pale, even though there is no actual [illegible]

[illegible] spells. They are often apathetic, avoiding strenuous games and exercise. Pollitzer[28] stated that a dry cough is commonly present but I have not observed cough, which was perhaps due to a high incidence of juvenile tuberculosis in the Vienna of the time. The musculature seems hypotonic and circulatory asthenia is often evidenced by cold extremities with patchy cyanosis. The carriage is often poor, there being a well-marked lordosis in the lower thoracic and upper two lumbar segments and frequently a protuberant abdomen (pot-belly) Varicocele is not rare. The proportion of children with orthostatic proteinuria who appear emotionally labile is high—some perhaps as a result of the reactions of the parents to the discovery of the proteinuria. But none of these findings is constant and [illegible]
sturdy childre [illegible]
liarities which have been considered as associated with benign proteinuria will be considered in the next section.

THE PATHOGENESIS OF ORTHOSTATIC PROTEINURIA

The question why protein should appear in the urine of individuals presenting no other evidence of disease has called forth a voluminous literature, in which unfortunately hypotheses have far outnumbered facts.

The view that orthostatic proteinuria is in reality a manifestation of true chronic nephritis was defended by Johnson[29] and others since. However, this conception is disproved by the fact that these individuals never show any of the typical manifestations of renal disease, such as edema, hypertension or impairment of renal function, even though they are followed for many years (see below). Maclean's (*loc. cit.*) extensive experience during World War I showed that soldiers with benign proteinuria had no greater incidence of trench nephritis than other soldiers. Heubner[30] reported an autopsy on an individual with orthostatic proteinuria, who died of an intercurrent cause, so far as I am aware the only one in the literature. There was no evidence of renal disease.

Another factor which has been considered as playing a part in the causation of some cases of benign proteinuria is focal infection, particularly in the lymphoid tissue of the throat, the teeth, and the accessory sinuses of the nose (Pollitzer, Calvin, Isaacs and Meyer). But, as the latter investigators point out, it is improbable that such chronic infections are ever the *sole* cause of benign proteinuria. For we see many patients with severe infections who have no proteinuria, and, on the other hand, many with benign proteinuria have no evidence of focal infection. Calvin, Isaacs and Meyer have seen the proteinuria in some instances clear up after the re-

left kidney which became larger. However, the proteinuria kidney. Bull found that of 18 ad been cystoscoped, including 3 of his own, the proteinuria was bilateral in 8 and 1 had proteinuria only

lordosis which appears when the individual stands ... probable that pronounced lordosis is concerned in the production of other cases of benign proteinuria. For one thing, not every child with benign ... lumbar lordosis, though the majority do.

patient had proteinuria when erect, but the protein disappeared from the urine when the patient reclined

Deficiencies in the General Circulation.—Deficiencies in the general circulation have long been thought by some to be concerned in the production of orthostatic proteinuria Some of the patients have striking vasomotor instability, and there may be abnormally great acceleration of the pulse on changing from the reclining to the erect posture Edel[11] called attention to the fact that the appearance of protein is accompanied by ... as the urinary volume rises. Thus, Lommel[12] found cardiac ... with orthostatic proteinuria

On the ... form ... cases t' ... posture and larger when reclining ...

Wessler[17] found that, while a considerable proportion of their cases had evidence of "relative" cardiovascular insufficiency, these symptoms were not associated in the great majority of cases with any hypertrophy or dilatation of the heart Thirty per cent of their patients had drop hearts I have seen no evidence of cardiac hypertrophy, many of the children have an overacting heart during the examination which, in combination with the thin chest wall, may have simulated cardiac hypertrophy in the eyes of older clinicians

Erlanger and Hooker[14] carried out very detailed studies of the circulation on a patient, aged twenty-seven years, with typical orthostatic proteinuria They demonstrated clearly that in this case the proteinuria was dependent

body had attained an angle of 40 degrees. If they eliminated the effect of

in many cases the production of a lordosis in the erect posture is the reason for the orthostatic nature of the proteinuria. When the child is in bed there is neither lordosis nor proteinuria. If the child rises from bed, lordosis appears and with it proteinuria. Should the child stay on its knees, a position in which lordosis is very marked, the proteinuria is especially pronounced. On the other hand, the proteinuria disappears if the child, when standing, *puts one foot on a stool*, which eliminates the lordosis despite the retention of the erect posture. Also, if the lordosis is corrected by means of an appropriate frame, there is no proteinuria in the erect posture. But if the lordosis is produced while the child is in bed by putting pillows under the back, proteinuria appears. Jehle quotes some interesting examples of how lordosis produces proteinuria in susceptible individuals. Thus, he observed one child in whom protein appeared every morning while still in bed; this was due to the fact that she combed her hair while in bed, an action that produces a marked lordosis. When her hair was combed by another person the proteinuria disappeared.

Jehle states that lordosis of the type he describes is found only at the time of life at which orthostatic proteinuria usually occurs. He believes the lordosis is produced by the vertebral column growing more rapidly than the rest of the body. Jehle found that while in normal children the distance from the vertebra prominens to the end of the sacrum is almost exactly one-third of the total length of the body, the length of the vertebral column in children with orthostatic proteinuria exceeds this proportion by several centimeters. He
and lax ligaments this
readily leads to a lordosis
Jehle observed that the excessive length of the vertebral column later became compensated by faster growth of the rest of the body, at which time the proteinuria disappeared.

Sonne[36] has made some interesting observations which afford support to Jehle's view of the significance of lordosis in the production of orthostatic proteinuria. He catheterized the ureters of 6 individuals with orthostatic proteinuria, the catheters remaining in place while the patient was either erect or a lordosis was produced in the recumbent posture. In 1 instance there was complete anuria for forty minutes; in 3 others left-sided anuria; while in the remaining 2 the urine from the left kidney was albuminous, in 1 instance containing as much as 2.6 per cent of protein In no case was the urine from the right kidney albuminous. In 2 patients with orthostatic proteinuria, whom I also saw, Beer[37] also proved cystoscopically that the protein in the urine came solely from the left side. It will be remembered that, inasmuch as the vena cava lies to the right of the mid-line, the left renal vein crosses over the vertebral column, from which it is separated by the aorta, a relatively hard structure. For this reason, Kelling[38] pointed out that if lordosis affects the kidney through mechanical interference with the venous return, the left kidney might preferentially suffer. Sonne's observations bear out this line of reasoning. It is also afforded some support by the studies of Rytand.[24] In two of his subjects with orthostatic proteinuria, diodrast appeared normally in both kidneys in the supine position; when they were erect, the diodrast was excreted in low concentra-

that is not uncommon in childhood. ... may show postural variations, increasing in the uria in orga ... from post- erect postu ... while the scarlatinal ... patient is in bed but albuminous when he rises. As ... emphasizes, all varieties of proteinuria may be influenced by posture. In proteinuria of nephritic origin, however, the quantity of protein in the urine is usually ... while in orthostatic proteinuria there is,

When the patient wakes the next morning, let him pass urine ... bed, this is free of protein in *orthostatic proteinuria*. Then have the ... either stand at attention or, even better, on his

than in the morning, a phenomenon which is the reverse of the rule in nephritic proteinuria

One should be very hesitant in diagnosing benign proteinuria if the twenty-four-hour urine contains more than a small amount of protein While the urine elaborated immediately after assuming the erect position may contain large quantities of protein (rarely even 1 per cent) in orthostatic proteinuria this does not continue, and the total day's urine

In benign proteinuria there is usually marked precipitation with dilute acetic acid in the cold But inasmuch as this reaction is absent in some cases of benign proteinuria and is not uncommon in organic renal disease, it

casts and even a moderate increase in the number of erythrocytes be brought out Large numbers of casts or many red cells, therefore, speak strongly for organic renal disease But it is to be remembered that there may be very few casts in proteinuria due to true nephritides.

THE PROGNOSIS OF ORTHOSTATIC PROTEINURIA

... and others, in the vast majority

gravity by having the patient stand in water or exerted a pressure of 50 mm. of mercury on the lower extremities by means of pneumatic trousers, there was no proteinuria in the erect posture. These experiments indicate the significance of circulatory factors in the production of the proteinuria. The investigators showed that increase in general venous pressure did not produce the proteinuria by having the reclining patient breathe against a high pressure until there was marked cyanosis; proteinuria did not appear. Erlanger and Hooker were further able to show that any procedure that lowered the pulse pressure favored the appearance of proteinuria in this patient, while any measure that increased the pulse pressure caused the proteinuria to diminish. In connection with this finding, they stress the conception that in experiments pulsatile filling of an organ is more efficient than constant filling, and that the glomeruli are particularly adapted to

. . : . . .. by Erlanger and Hooker in this patient, they evidently do not explain most cases of orthostatic proteinuria, for Bass and Wessler[27] found that there is little difference between the blood pressure of children with orthostatic proteinuria and normal children. I have seen no evidence that deficiencies in the general circulation play any part in the causation of orthostatic proteinuria

General Discussion.—Orthostatic proteinuria results from an impediment to the venous return from the kidneys, which is present in the erect posture and disappears during recumbency In many cases the venous engorgement which produces the proteinuria is confined to the left kidney and results from compression of the left renal vein against the aorta by lumbar lordosis which is accentuated in the erect posture. In others, the lordosis compromises the inferior vena cava with resultant bilateral venous engorgement and proteinuria. Bull[51] has made observations which he interprets as indicating that the compression of the inferior vena cava by the lordotic spine is against the posterior surface of the liver.

The causative lordosis is apparently of constitutional origin and correlated with the period of rapid growth in height; it almost invariably disappears after this period. There may be other mechanisms (*e.g.*, ptosis) which kink a renal vein in the erect posture and thus produce proteinuria, but these are not yet understood. There is no evidence that infection plays any part in the pathogenesis of orthostatic proteinuria

THE DIAGNOSIS OF ORTHOSTATIC PROTEINURIA

The diagnosis of benign proteinuria is of the highest importance so that true nephritides may not be neglected or, what is surely much more common, healthy children be subjected to unnecessary restraint which interferes with their normal development Unfortunately, the differentiation of orthostatic proteinuria from organic renal disease is often a matter of great difficulty, requiring a long period of observation In many cases which ultimately clear up, one is never sure with which he is dealing

The presence of arterial hypertension, edema or impaired renal function speaks immediately for the diagnosis of an organic lesion of the kidney. The difficulties lie in the differentiation of orthostatic proteinuria from those

cases of renal disease which for long periods show no symptoms other than proteinuria and slight microscopic urinary abnormalities, a type of case that is not uncommon in childhood It is to be remembered that proteinuria [illegible] may show postural variations, increasing in the erec[illegible] from post- [illegible] while the scarlatina[illegible] patient is in bed but albuminous when he rises. [illegible] emphasizes, all varieties of proteinuria may be influenced by posture. In proteinuria of nephritic origin, however, the quantity of protein in the urine is usually distinctly increased by exercise, while in orthostatic proteinuria there is, as a rule, less protein when the patient walks about than when he stands still But the difference is rarely great enough to be of practical value.

The relations of the proteinuria to posture may be studied as follows: Let the patient empty his bladder an hour after going to bed so that no urine formed while still erect should be included in the morning specimen. When the patient wakes the next morning, let him pass urine while still in bed, this is free of protein in orthostatic proteinuria. Then have the [illegible] either stand at attention or, even better, on his [illegible]

[illegible] than in the morning, a phenomenon which is the reverse of the rule in nephritic proteinuria.

One should be very hesitant in diagnosing benign proteinuria if the twenty-four-hour urine contains more than a small amount of protein While the urine elaborated immediately after assuming the erect position may contain large quantities of protein (rarely even 1 per cent) in orthostatic proteinuria this does not continue, and the total day's urine rarely contains more than 0 2 or 0 3 per cent of protein and usually considerably less Large amounts of protein in the twenty-four-hour specimen speak strongly for organic disease

In benign proteinuria there is usually marked precipitation with dilute [illegible] little diagnostic value

The urinary sediment in benign proteinuria contains comparatively few or no casts and at most a few red blood cells. Only if the subject stands in a position of exaggerated lordosis can quite numerous hyaline and granular casts and even a moderate increase in the number of erythrocytes be brought out Large numbers of casts or many red cells, therefore, speak strongly for organic renal disease But it is to be remembered that there may be very few casts in proteinuria due to true nephritides.

THE PROGNOSIS OF ORTHOSTATIC PROTEINURIA

[illegible] by Dukes, Heubner and others. In the vast majority

of the cases the proteinuria had disappeared. None of these studies afford any evidence that orthostatic proteinuria leads to disease of the kidney later in life. Jehle states that in only 3 cases of a very extensive experience did he observe orthostatic proteinuria become continuous, but does not mention that actual symptoms of renal disease developed. Fox[47] found no evidence of subsequent renal disease in any of the 20 cases of orthostatic proteinuria that he detected during life insurance examinations, though 13 of them were examined as long as thirty years after the proteinuria was originaly detected. Maclean's[7] extensive investigation during World War I showed that recruits with benign proteinuria did not have a higher incidence of trench nephritis than other troops. Orthostatic proteinuria must, therefore, be considered as harmle[illegible] ...ce on the duration

[illegible] Thus, Gulland[49] states that if the proteinuria is orthostatic he does not rate the applicant up. Fox[47] also accepts applicants with benign proteinuria at ordinary rates for a twenty-five-year policy, but asks a small advance for a whole life policy. In the writer's opinion this is unjustified.

It is impossible to answer with any assurance the usual question of parents of children with orthostatic proteinuria as to how long the proteinuria will last. All that can be told them is that no matter how long it lasts, it will never do any harm and will ultimately disappear. In some cases the condition clears up soon after being noted, but in the majority it does not disappear until during or shortly after puberty. Cases are known in which the proteinuria has been followed for as much as fifteen years after puberty (Martius[21]), but such a long duration seems to be unusual. When the orthostatic proteinuria noted in young adults had its inception has not, to my knowledge, been investigated.

THE TREATMENT OF ORTHOSTATIC PROTEINURIA

Once the diagnosis of orthostatic proteinuria has been established, the patient needs no treatment. Above all, neither rest nor dietetic treatments should be attempted. It is highly improbable that they exert any [illegible] child should be allowed to play [illegible] It may be difficult to reassure the parents to prevent their coddling the child with the inevitable deleterious effects of such a procedure. Neurotics must not be created. In the vast majority of instances, the child would undoubtedly be better off if the proteinuria were never discovered.

If the child has a marked lordosis, exercises designed to strengthen the trunk muscles may be prescribed, but in general the best exercise is normal play. Jehle has designed a frame to correct the lordosis. I have not seen the device used, but it seems totally unnecessary in view of the harmlessness of the proteinuria. Wearing such an apparatus may create a feeling of inferiority in the child with consequences infinitely worse than those of the proteinuria

Nassau,[49] Post and Thomas[50] and others have found that alkalinization of the urine with sodium bicarbonate will often cause the proteinuria to

disapp... But the proteinuria returns if the alkalinization is discontinued, so the ... the procedure. Atropine, calcium and o...
of no practical ...
static proteinuria to whom I gave enough sodium bicarbonate ...
the urine there is was no definite effect on the amount of protein excreted. ... tonsils carious teeth, or the

...

static proteinuria, for there is no evidence ...
relation to the latter or that their removal will render the urine noncoagu-

...

... tial diagnosis between ortho...

to be no good reason for putting them to bed, or keep...
during the period of observation. While efforts should be made to minimize exposure to inclement weather and respiratory infection, and perhaps oral prophylactic doses of penicillin administered, one should be careful not to induce an anxiety state in the child or its parents.

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Chapter
15

THE NECROTIZING NEPHROSES

DURING recent years, three circumstances especially have combined to widen interest in a family of nephropathies characterized clinically by an acute course with extreme oliguria and anatomically by necrosis of the tubular epithelium:

1 More frequent transfusion has unfortunately brought in its wake an increase in the number of individuals receiving incompatible blood.

2 Sulfonamide therapy introduced a potent and for a time common source of renal tubular damage.

3 The battle injuries and civilian bombings of World War II furnished an enormous contingent of patients with renal damage consequent on trauma Indeed, it was Bywaters and Beall's[1] description, under the name

owing injuries in the

sion generally on the

In an important study of the extensive material of World War II at the Army Medical Museum, Lucké[2] integrated the different etiologies of acute renal necrosis under the designation *lower nephron nephrosis*. Lucké coined this term because he found that the same regressive lesions in the lower nephron which Dunn and his coworkers[3] had originally observed in the crush syndrome occur as a result of a variety of etiologies: "severe trauma to muscle, nontraumatic muscular ischemia, burns, transfusion with incompatible blood, heat stroke, blackwater fever, toxemias of pregnancy and uteroplacental damage, alkalosis, sulfonamide intoxication, and poisoning with certain vegetable and chemical agents." By "lower nephron" Lucké means the ascending (thick) limb of Henle's loop and the distal convoluted tubule The term lower nephron nephrosis has attained wide currency However, in the following the term *necrotizing nephrosis* will be used because the circumstances have not yet been established in which the damage is actually confined to the lower nephron. For instance, in hemoglobinuric nephrosis, which has been reckoned as a lower nephron nephrosis, the proximal convoluted tubule may be most ... ected.

ubule

most

bule is

segments of the tubule. The clinical picture of

necrotizing nephrosis due to mercury poisoning, which affects predominantly the proximal convoluted tubule, does not differ from that of post-traumatic anuria, in which the lesions may affect any part of the tubule.

For these reasons the term lower nephron nephrosis does not seem adequately based.

The necrotizing nephroses are many and diverse. But while the etiologic varieties have individual clinical and anatomic characteristics, there are fundamental features common to all.

Clinical Picture.—The clinical picture of all forms of necrotizing nephrosis is dominated by rapidly progressive impairment of renal function. An outstanding characteristic is an early and abrupt fall in urinary volume,

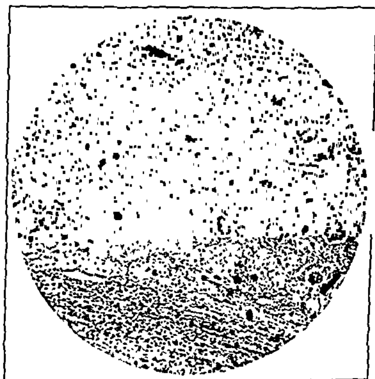


Fig 10—Necrotizing nephrosis with secondary calcification complicating peritonitis The calcified masses appear black

which often goes on to anuria In the necrotizing nephroses of renal origin, *e. g.*, mercury poisoning, hyposthenuria is present from the onset. Contrariwise, in those renal necroses which are of prerenal origin, *e. g.*, traumatic shock, the specific gravity is high during the initial stage of isolated impairment of glomerular filtration and then falls as the tubules are damaged The renal failure produces uremia. However, uremic symptoms may become distressing only after a deceptive latent period of several days during which the patient feels well. Hypertension is absent at the onset but often appears after several days; while often only modest, exceptionally it exceeds 210/120 mm. Edema generally is absent unless considerable volumes of fluid are administered. The mortality is considerable in most

forms of necrotizing nephrosis. If recovery is to occur, it is most often heralded by increase in urinary volume, which may go on to tremendous polyuria. Hyposthenuria may last for months during which the patient feels well. The writer has not encountered any cases in which it seemed clear that necrotizing nephrosis went on to chronic renal disease; either death ... recovery has occurred However, the possibility that necro...

clude...

In cases ... ment, which suggests that with survival scarring would result.

An excellent and detailed study of the clinical picture of necrotizing nephrosis has recently been published by Swann and Merrill.[11]

Pathological Anatomy.—The characteristic lesions are regressive changes in the tubular epithelia which go on to necrosis. Various segments may be affected predominantly. Individual parts of the tubule may be affected with selective intensity in the different etiologic varieties of necrotizing ... be learned of the topographic characteriza-

... is extensive in some but not all varieties of necrotizing nephroses ... tubular edema and cellular infiltration often develop secondarily. Glomerular lesions are not prominent, but frequently the presence of protein in Bowman's space bespeaks increased permeability of the loops.

... feasible much more accurate localization in the nephron than does the study ... lesion occur ... "The first ... the proximal convolution, which is functionally concerned with the handling of the poison. Since poisons are distributed by the renal circulation all nephrons are equally involved. The second type of lesion is a disruption of the renal tubule (tubulorhexis) due to focal cortical ischemia It occurs at random among nephrons and in any part of a nephron." Oliver's preparations show clearly that in this second lesion there is solution of the continuity of the tubular wall by discrete and more or less numerous and extensive foci of epithelial necrosis with rupture of the underlying basement membrane. He observed that the tubular cells may be remarkably well preserved right up to the necrotic segment For many features of the morphology of the necrotizing nephroses, which are revealed only by study of individual nephrons in continuity, the reader is referred to the unique publication of Oliver and his associates, which to the writer seems a classic of the morphology of the diseased kidney

Pathogenesis and Pathological Physiology.—Four main processes enter

2. Injury to the tubular cells by substances entering them from the glomerular filtrate or blood stream. Included are not only readily diffusible bodies such as mercuric chloride or sulfonamides, but also such large molecules as hemoglobin and its derivatives, which are taken up by the tubular cells and damage them by mechanisms yet to be elucidated. That it is predominantly the entry into the tubular cells of such substances as mercuric chloride from the glomerular filtrate rather than from the blood stream which is responsible for the epithelial damage is shown by experiments in which filtration in one kidney is stopped by ureteral ligation; the necrotizing nephrosis then affects only the contralateral organ.

3. Blockage of tubular lumens by such substances as heme pigments or sulfonamide crystals, which either form large conglomerates or so increase the viscosity of the tubular fluid as to impede its flow.

4. Secondarily to the tubular damage there occur edema and sometimes cellular infiltration of the intertubular tissue. The resultant swelling and increase in intrarenal pressure may be significant in decreasing renal blood flow and consequently glomerular filtration (*cf.* Peters[6]).

The importance of these factors doubtless varies greatly in individual necrotizing nephroses and in different stages of the same process. Thus, in traumatic shock decrease in renal blood flow with slowing of glomerular filtration inaugurates the pathogenetic chain; tubular damage with hyposthenuria follows only later. Contrariwise, in mercury poisoning solely the factor of damage to the tubular epithelia operates at the start; only later does swelling interfere with the renal circulation.

Characteristic of the renal insufficiency in necrotizing nephrosis—and hardly if at all encountered in other conditions—is that augmented and nonselective tubular back-diffusion is *one* of the participating factors.* In the chemical nephroses, augmented back-diffusion is doubtless the *initiating* factor in the pathogenesis—leading to what was above called regurgitation uremia (p. 37). Richards[7] demonstrated this by direct observations on frogs poisoned with mercury. He observed that filtration continues at a rate even faster than normal, but no urine issues from the tubules; apparently all the filtrate is drawn through the necrotic tubular walls back into the blood by the osmotic pressure of the plasma proteins. Dyes to which the tubular cells were normally impermeable entered these cells from the lumen after they had been poisoned by mercury. Hayman[8] and his coworkers demonstrated the occurrence of tubular back-diffusion in dogs in whom necrotizing nephrosis had been produced by uranium salts. They found that the inulin and creatinin clearances and extractions were greatly depressed although renal blood flow (measured by the Fick principle from the renal arterio-venous creatinin and inulin differences) were only negligibly changed. In some of their observations, there was a

* The anatomical basis for the regurgitation of tubular fluid into the blood in necrotizing nephrosis is revealed
dissection of individual nep
course of the intact tubule,
is broken, frayed or disintegrated and the epithelial lining disrupted and necrotic. The result is a solution of continuity The lumen thus lies open to the intertubular interstitial tissue and its capillaries and veins."

negative diodrast Tm (p 38), *i. e*, more diodrast was filtered than was excreted, thereby demonstrating the tubular back-diffusion of this substance, which is normally excreted with remarkable efficiency by the tubules It was mentioned above (p 52) that a few observations have been recorded of a negative Tm in human necrotizing nephrosis. Unfortunately, these findings of a negative Tm have been obtained by clearance methods, which lack absolute validity in the presence of tubular necrosis (p. 24), but they nevertheless indicate strongly that tubular back-diffusion has occurred

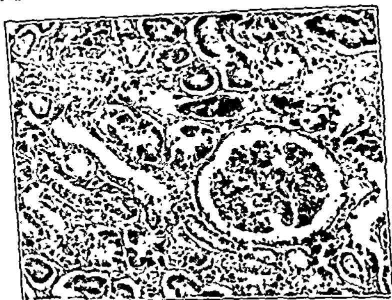


FIG 11 —Necrotizing nephrosis in a postoperative patient who succumbed with renal insufficiency (oliguria going on to anuria, NPN 200 mg per cent, terminally uremic frost) *

Decrease in kidney blood flow also participates in producing the renal insufficiency of necrotizing nephrosis It is the primary factor in necrotizing nephrosis of prerenal origin (p 79), but also occurs in the later stages of the chemical nephroses Since the glomeruli show little change, fall in renal blood flow presumably occurs when swelling of the kidney due to intertubular edema and cellular infiltration elevate intrarenal pressure But obstruction of tubules by casts may also participate through producing internal hydronephrosis of the affected nephrons, which hampers renal blood flow and impedes glomerular filtration Decreased renal blood flow was demonstrated in experimental mercury poisoning by Linder and Sarre[9] The clearance studies of Corcoran, Taylor and Page[10] indicated decreased renal blood flow in human carbon tetrachloride and mercury poisoning. By catheterization of the renal vein Sirota[11] demonstrated that renal blood flow and glomerular filtration are greatly diminished in the later stages of human carbon tetrachloride nephrosis. His earliest

* I am greatly indebted to Dr William Antopol, Director of Laboratories of Beth Israel Hospital, for Figures 11, 17, 18, 27, 33, 34, 35 and 49

measurements were eight days after the onset of oliguria; in 1 case renal blood flow was only 40.8 cc. per minute. In 33 patients with necrotizing nephrosis due to ingestion of poisons, intravascular hemolysis, shock and other causes, Bull, Joekes and Loew[12] studied renal blood flow by PAH clearance and renal vein catheterization. They found renal blood flow grossly reduced during the oliguria; with improvement, it then steadily increased and reached normal levels in from three to nine months. In these observations, glomerular filtration showed reduction of the same order as blood flow. That all the functions of the tubule are depressed in necrotizing nephrosis, as would be anticipated from the anatomical findings, is indicated by these studies of Bull, Joekes and Loew with renal vein catheterization and clearance methods. During the oliguric phases of necrotizing nephrosis, they found "inability of the kidney (1) to concentrate urea and creatinin, (2) to conserve sodium, chloride and potassium, (3) to extract PAH from the blood, and (4) to reabsorb glucose at a normal rate."

In most instances of necrotizing nephrosis, two stages of impairment of renal function succeed one another: (1) An initial *oliguric stage* due to excessive passive back-diffusion of filtrate and perhaps decreased glomerular filtration; and (2), a *diuretic stage* due to impairment of active tubular reabsorption.

Long after symptomatic recovery from necrotizing nephrosis, evidence of damage to tubular function persists. There may be hyposthenuria for months or even more than a year. Hunter and Muirhead[133] observed 2 cases in which salt wastage lasted for forty-four and sixty days after the onset; the total urinary chloride excretion varied between 20 and 48 grams of NaCl. It is important that this salt-losing tendency be combatted during convalescence.

MERCURIAL NEPHROSIS

As far back as 1519, Ulrich von Hutton[13] was aware that mercurial intoxication may be manifested by anuria. Up to twenty years ago mercury poisoning was a common cause of necrotizing nephrosis. But with the replacement, in New York City at least, of bichloride of mercury by barbiturates as the favorite means of committing suicide, mercurial nephrosis has become infrequent. The outspoken clinical or anatomical picture of necrotizing nephrosis hardly occurs in chronic mercurial intoxication, being seen after a single large dose of bichloride of mercury taken by mouth either accidentally or with suicidal intent, or vaginally as a douche or abortifacient. However, Munk's[14] observation that calcified foci are not uncommonly found in kidneys of old syphilitics indicates that the therapeutic use of mercury can cause similar lesions, though of slighter degree. Rarely, calcific foci are also present in the kidneys of patients who have had mercurial diuretics.

Pathological Anatomy.—In fatal cases of mercurial nephrosis the kidneys are enlarged, smooth and soft. As a rule, they are grayish-white and anemic, but Askanazy and Nakata[15] state that in the rare cases that die within the first day after the poisoning and those succumbing after the eighth day, the kidneys may be red and congested.

... the tubular epithelium ... lesser involvement ... proximal ...

of regeneration The lumen of the tubule ... extreme cloudy swelling and vacuolar degenerat... by the necrotic ... fatty change. ... apart from frequent ...

A remarkable phenomenon is the calcification ... cells long ago described by Saikowsky.[19] It is present in most, though not all, cases in which death occurs after the first days. Calcification of the ... not diagnostic of mercury poisoning, it occasionally ... When intesti... ...) are ac... Zeman and his associates[20] observed calcification as early as ... day of necrotizing nephrosis in experimental pyloric obstruction in cats. Among the other causes of calcification of the renal tubules listed by Derow[21] are Vitamin A deficiency, ingestion of an excess of inorganic phosphate, ... mercurial ...

... hematoxylin ... present as th...

The cause ... much greater than in necrotizing nephrosis due to other heavy metals, is not clear It is not due to increased calcium content of the blood, for this is not present The normal or low calcium concentration in the blood also speaks strongly against the hypothesis of Schmidt,[23] who attributes the renal calcification to the frequently coexistent mercurial colitis, which throws a heavier burden in calcium excretion on the kidney

... as to surround the latter completely The regenerated cells stand out in the section because of their deeply staining nuclei. They may form giant cells Heineke believes that the regenerated epithelia participate in the removal of the dead cells Around the necrotic masses are also polymorphonuclear leukocytes which evidently act as phagocytes. Removal

* Injection of mercury into various mammals and the frog likewise produces selective necrosis of the proximal tubule (Suzuki,[16] Edwards[17]).

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Red blood cells are most often scanty or absent, but may at times appear in moderate numbers in the sediment. Nor are leukocytes conspicuous.

The volume of urine diminishes, and in many cases complete anuria [illegible] can be obtained by catheterization.

[illegible]

The predominant mechanism in the pathogenesis of [illegible] insufficiency is doubtless nonselective back-diffusion of the glomerular filtrate through the necrotic tubular wall.

[illegible] anuria or extreme oliguria, there is often a [illegible]

[illegible] was present in but 1 of Rosenberg's[27] 14 cases [illegible] demonstrates clearly the incorrectness of the view, once widely held, that [illegible] hypertension is absent in some cases, but [illegible]

[illegible] ing nephrosis. In one patient the blood pressure [illegible] within four days The changes in blood chemistry are those found in all forms of renal insufficiency (Chapter 3). The chloride content of the plasma, unless influenced therapeutically, is sometimes remarkably low (Lewis and Rivers,[28] Kilban[29]), this is perhaps due to electrolyte loss from [illegible] intestinal tract being added to the uremic [illegible]

[illegible] injury to the concentrating power of the kidney Hyposthenuria may [illegible]

[illegible] in which [illegible] (if obtainable) and stools should be examined for mercury [illegible], the urine [illegible] Lambert and Patterson[30] state that mercury appears in the urine in from three to twenty-four hours after it has been swallowed

The postmortem demonstration of mercury in the organs may be of medico-legal importance It has been found that the kidneys contain the greatest concentration of mercury, but that the largest absolute amount is in the liver (Sollman and Schreiber)

Prognosis [illegible] ingested and [illegible] is instituted [illegible]

of débris and regeneration proceed very rapidly. Thus, in a case of bichloride poisoning studied by Hunter,[25] in which death occurred on the fourteenth day from pneumonia and the intestinal lesions, there had been almost complete regeneration of the tubular epithelium. In cases of some standing, there may be a moderate degree of interstitial proliferation.

Clinical Picture.—The ingestion of large quantities of bichloride of mercury in tablets or solution is followed by a metallic taste in the mouth and abdominal pain. Usually, there is vomiting, the vomitus often containing blood and mucus. In most cases, stomatitis and bloody diarrhea with severe tenesmus then appear.

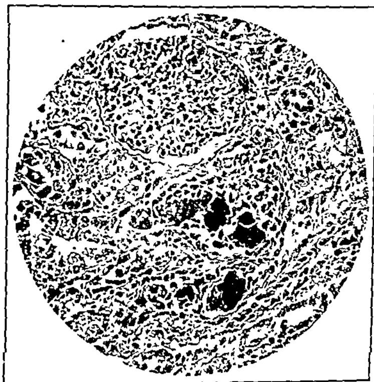


Fig 12.—Necrotizing nephrosis with secondary calcification in mercury poisoning. The tubular cells are in various stages of degeneration and necrosis. The dark masses are calcified epithelia.

At any time, from a few hours to about three days, after the mercury has been taken, proteinuria and marked oliguria or anuria appear. In cases in which only small amounts are absorbed, there may be proteinuria with polyuria, I saw one such case which quickly recovered.

After the proteinuria has appeared, such little urine as is passed is generally cloudy. Hyposthenuria quickly appears and the specific gravity does not vary much from 1.010. The quantity of protein is rarely great, and it may be only a small fraction of 1 per cent. Hyaline, granular and epithelial casts are present as well as numerous epithelial cells and granular débris evidently derived from necrotic cells. According to Munk,[26] doubly refractile lipoids are never found, in sharp contrast to chronic nephrosis

That BAL affords a high degree of ... was shown in experimental animals by Gilman et al.,[a] Stocken[a] and others ... BAL interferes with the effects of mercury on the tubular ... the finding of Sussman ... The remarkable effects ... n by the well controlled studies of Longcope and Luetscher ... control patients who had ... were treated within four ...

It is of the utmost importance that BAL be injected ... there is irreversible damage to the kidneys. The drug is supplied in 20 per cent benzylbenzoate in peanut oil and given intramuscularly. The initial dose is about 3 mg./kg. With desperately ill patients 5 mg./kg. may be given. The larger dose often produces transitory disagreeable by-effects such as nausea, vomiting, headache, tremulousness and paresthesias. ... transitory hypertension; in one patient the blood ...

In the general management of patients with ... same principles are followed as in other forms of acute renal insufficiency (p. 225). Of primary importance is the alleviation of dehydration, the tendency to which in mercurial nephrosis may be especially great because of vomiting and diarrhea due to ulcerative lesions of the gastro-intestinal tract. But once dehydration has been relieved, fluid and salt should be administered only in quantities sufficient to maintain the volume and composition of the extracellular fluid. In the past forcing of sugar and salt solutions was often carried to the point of producing pulmonary and cerebral edema and heart failure. Anemia is to be combatted by transfusion of blood and hypoproteinemia by plasma; these should be carried out with especial caution because of the susceptibility of the patients to heart failure.

The artificial kidney, peritoneal lavage and other methods for augmenting ...

... which dec... covered, of ... survived ... results do not seem better than those obtained by conservative measures even in the worst cases. I have not seen recovery in mercury poisoning treated by decapsulation and do not advise the operation.

Rybak and Stern[a] have observed the onset of diuresis in anuric cases of mercurial nephrosis following irradiation of the kidneys with small

mercury or were immediately effectively lavaged recovered (*cf.* Lambert and Patterson,[30] Rosenberg[17]), almost all those who ingested large quantities succumbed unless they vomited the tablets or had them immediately washed out. Thus, Longcope and Luetscher[31] state that 8 of 9 patients, who took 3 grams or more of mercuric bichloride and were not treated with BAL, died. On the other hand, all four of their patients who took 3 to 20 grams of bichloride and were treated with BAL recovered.

Anuria is a serious omen. However, even before BAL, recovery had been observed after five or even more days of anuria. While the onset of diuresis generally is followed by complete recovery, in rare instances death in uremia occurs. This may be due to the urine being of such low concentration that increased volume does not avert renal insufficiency. Salt depletion may participate in producing a fatal outcome during the diuretic phase.

When recovery from mercurial nephrosis occurs, no permanent injury to the kidney seems to remain. The proteinuria usually disappears within a few weeks, but the impairment of concentrating power may last for months before it disappears completely.

Treatment.—The past few years have witnessed a gratifying improvement in the efficacy of treatment for mercurial nephrosis. This is due primarily to the introduction of BAL. But even before this, there had been some improvement in the results because of better management of water and electrolyte balance.

As quickly after the ingestion of the mercury as possible, the patient should be given several raw eggs in milk to precipitate any mercury in the stomach, and the stomach washed thoroughly. Sollman, Barlow and Biskind[32] point out that if milk is not available, it is advisable to administer half a glass of water before the eggs, to prevent the latter from cementing the bichloride tablets to the stomach. A vigorous cathartic should be given.

Rosenthal[33] has introduced *sodium formaldehyde sulphoxylate* as an antidote for acute mercury poisoning. This compound reduces bichloride of mercury to the mercurous form or metallic mercury. If available, sulphoxylate should be used for the initial lavage Rosenthal advises that the stomach be washed with a 5 per cent solution of sulphoxylate and about 200 cc of the solution left in the stomach. Immediately after this, 10 gm. of sulphoxylate dissolved in 200 cc. of water is given by very slow intravenous drip; this may be repeated about six hours later If colitis develops, Rosenthal gives high colonic irrigations once or twice daily with a 1 to 1000 solution of sulphoxylate. The treatment is claimed to be effective when instituted up to about an hour and a half after ingestion of the bichloride. On the basis of their animal experiments, Brown and Kolmer[34] advise that smaller amounts should be given intravenously, the main value of the sulphoxylate appears to be in its reducing action on the bichloride in the stomach and gut which it reaches by early oral administration.

The treatment of mercurial nephrosis has been revolutionized by the introduction of British Anti-Lewisite (BAL, 2,3-dimercaptopropanol). This dithiol was originally introduced as an antidote for Lewisite, and has proved to be the most effective available remedy for poisoning by arsenic, mercury, gold and perhaps some other metals (but apparently not lead).

to anuria The urine contains protein, ...

ably smaller.

Treatment.—After ingestion of the chemical, the stomach should be washed out and a saline cathartic given. Respiratory depression may call for artificial respiration and injections of caffein sodium benzoate. Because of the liver damage as much carbohydrate as possible should be given; parenteral administration is generally necessary. But because the chief danger to life is renal rather than hepatic failure, the advisability of at-

...tein and amino acids, as in other

The treatment of the acute renal

223)

SULFONAMIDE NEPHROSIS

In the heyday of sulfonamide therapy, renal insufficiency was a redoubtable and not extremely rare complication which led to many deaths. The sulfonamides bring about renal failure through two mechanisms:

1. **Obstruction by Sulfonamide Crystals.**—Precipitation and conglutination of sulfonamide crystals may block the flow of urine anywhere from Henle's loop to the ureter; even vesical calculi may form. Crystals are rarely found proximal to Henle's loop where the major concentration and acidification of the glomerular filtrate occurs. By administration of sulfonamides to animals Antopol and Robinson[32] showed that precipitation and blockage may occur in a previously healthy urinary tract. There are four main factors which condition the likelihood of sulfonamide crystalluria

the compara-

o close paral-

l the liability

soluble than

...ost invariable

unless the urine is alkalinized. This was indicated by patients in whom subacute bacterial endocarditis was treated by deliberate production of exorbitantly high sulfadiazine levels in the blood; pronounced azotemia

... with its entailed increase in

...ators precipitation of sulfonamides. Crystalluria is hardly to be feared if the daily urinary volume

doses of roentgen rays. I have no experience with the method of treatment which has no logical basis.

CARBON TETRACHLORIDE NEPHROSIS

Necrotizing nephrosis due to inhalation or ingestion of carbon tetrachloride has been encountered with fair frequency in recent years, since the chemical has been widely used as a cleaning fluid and in industry. Alcoholism seems to favor the development of the intoxication. The initial manifestations of acute poisoning are varied. They may include nausea, vomiting and diarrhea; the diagnosis of acute gastro-enteritis may be made in the absence of a history of inhalation or ingestion of the poison. Sometimes there is vertigo, lassitude and somnolence, and the patient may be regarded as drunk. [illegible]
headache, convulsions, [illegible]
hematemesis. Within tw [illegible]
be revealed by jaundice. Oliguria sets in and uremic symptoms develop. Sometimes a hemorrhagic diathesis appears Occasionally the initial symptoms are not pronounced or misinterpreted, and the possibility of carbon tetrachloride poisoning is not considered until renal insufficiency is evident. It is possible that the etiological role of carbon tetrachloride has been overlooked in some cases of necrotizing nephrosis (*cf.* Farrier and Smith[38]). While many of the patients are desperately ill, the large majority recover; a fatal outcome is usually due to uremia. Smetana[39] found symptoms of renal insufficiency in 33 of 141 cases of acute carbon tetrachloride poisoning, and pointed out that the kidneys are more apt to be implicated when the poisoning is by inhalation.

The *anatomical changes* are those of necrotizing nephrosis. The glomerular tufts show little change Bowman's space is often widened and contains protein; the lining cells may be swollen. The outstanding findings are regressive changes in the tubular epithelium going on to necrosis and desquamation. There are large numbers of casts (not heme) and much epithelial débris in the tubular lumens. In 2 cases carefully studied at necropsy by Smetana, both the proximal and the distal segments of the tubules exhibited regressive changes, but the necrotizing process was more severe in the distal portions. There is intertubular edema and cellular infiltration In cases succumbing toward the end of the first week, regeneration of tubular epithelial cells is evident.

The detailed studies of Corcoran *et al.* and Sirota on the *pathogenesis* of the renal insufficiency have already been mentioned (p. 413). They indicate that both tubular function and renal blood flow are severely impaired. Sirota's findings indicate that unselective tubular back-diffusion is the predominant factor in the earlier stages of the azotemia, while subsequently decrease in renal blood flow (due to swelling) becomes more significant.

The *clinical picture* is that found in all forms of acute renal insufficiency, complicated by the effects of carbon tetrachloride on the liver, gastrointestinal tract and central nervous system, as well as sometimes by a hemorrhagic diathesis. However, the symptoms other than those due to renal failure tend to clear up rapidly; the result is that most often one is

confronted predominantly by the mani
sis. Hypertension is the rule and in
Edema
progres

In the 141 cases collected by Smetana, there ... lethal cases are more apt to be reported, so that the mortality rate is probably smaller.

Treatment.—After ingestion of the chemical, the stomach should be washed out and a saline cathartic given Respiratory depression may call for artificial respiration and injections of caffein sodium benzoate. Because of the liver damage as much carbohydrate as possible should be given; parenteral administration is generally necessary. But because the chief danger to life is renal rather than hepatic failure, the advisability of at- ... tein and amino acids, as in other ... The treatment of the acute renal insufficiency is discussed ... 223)

SULFONAMIDE NEPHROSIS

1 **Obstruction by Sulfonamide Crystals.**—Precipitation and conglutination of sulfonamide crystals may block the flow of urine anywhere from Henle's loop to the ureter, even vesical calculi may form Crystals are rarely found proximal to Henle's loop where the major concentration and acidification of the glomerular filtrate occurs. By administration of sulfonamides to animals Antopol and Robinson[44] showed that precipitation and blockage may occur in a previously healthy urinary tract There are four main factors which condition the likelihood of sulfonamide crystalluria

(*a*) *The Blood Level* —This is determined by the dose and the comparative rapidity of absorption and excretion While there is no close parallelism between the amount of sulfonamide administered and the liability to urolithiasis, with sufficiently high doses of a drug no more soluble than sulfadiazine precipitation in the urinary tract is probably almost invariable unless the urine is alkalinized This was indicated by patients in whom subacute bacterial endocarditis was treated by deliberate production of exorbitantly high sulfadiazine levels in the blood, pronounced azotemia almost always developed

(*b*) *The Urinary Concentration* —Oliguria with its entailed increase in concentration of the urinary constituents favors precipitation of sulfonamides Crystalluria is hardly to be feared if the daily urinary volume

can be maintained above 1500 cc. Many instances of sulfonamide blockage are due primarily to oliguria resulting from fever, vomiting and inadequate fluid intake.

(c) *The Reaction of the Urine.*—Alkalinization of the urine averts crystalluria due to sulfadiazine or sulfathiazole. Gilligan[40] and his associates observed that acetylsulfadiazine is 6 times as soluble at pH 6.5 as at pH 5.2. Fox[41] *et al.* found that as the pH of the urine is increased, there is a sudden great rise in the solubility of these sulfonamides and their acetyl derivatives when the urine becomes alkaline. They state that this is because sulfadiazine and sulfathiazole as well as their acetyl compounds are weak and but slightly soluble acids which ionize and form soluble sodium salts in an alkaline medium. On the other hand, Fox and his associates found that sulfapyridine did not undergo extensive salt formation at any physiological pH, which accounts for the failure of alkalinization to prevent precipitation of sulfapyridine.

(d) *The Solubility of the Sulfonamide.*—This is the most important factor. Obstructive precipitation did not occur in the early days of sulfonamide therapy when [illegible] encountered [illegible] which are but [illegible] degree of acetylation (largely in the liver) with the production of even less soluble acetyl conjugates. When the somewhat more soluble sulfadiazine came into use, it was hoped that obstruction by precipitated crystals would be eliminated, but this hope proved illusory and many cases of fatal sulfadiazine urolithiasis were observed. Lehr[42] attempted to prevent urinary precipitation by the introduction of sulfonamide mixtures. He found that different sulfonamides are independently soluble in urine, so that more of a mixture (*e. g.*, sulfadiazine, sulfamethazine, sulfacetamide and sulfamerazine) can be held in solution than of any one alone. However, the quantitative advantages of sulfonamide mixtures are not great and equal to alkalinization of the urine (Garb and Janoff[43]). Almost complete solution of the problem of precipitation has been achieved by the synthesis of highly soluble and therapeutically effective sulfonamides such as Gantrisin and sulfacetamide; the latter is 80 times as soluble as sulfadiazine (Lehr[44]). Brinkhouse[45] *et al.* treated 142 patients with Gantrisin and observed gross hematuria in 1 and crystalluria in 1 other. Bigler and Thomas[46] detected neither crystals nor red cells in the urine of 71 children treated with Gantrisin.

In the past few years, renal insufficiency due to sulfonamide crystallization has become a rarity; the writer has not seen a case in at least three years. This is due partly to displacement of sulfonamides by antibiotics; formerly, when sulfonamides did not produce therapeutic results, the dose was often increased despite acid oliguria and precipitation followed. Even more important has been the introduction of the highly soluble sulfonamides and the appreciation of the importance of adequate urinary volume and alkalinization.

2. **Necrotizing Nephrosis Due to Sulfonamides.**—The symptomatology of urinary obstruction by sulfonamides with its renal colic and gross hematuria is often so spectacular that this was at first considered the only

pathogenesis of renal damage by sulfonamides. However, it was soon pointed out by Long *et al.*[17] that sulfonamides may produce renal insufficiency, in the absence of obstruction by crystalline masses, as a result of cytotoxic action on the renal epithelia. Cases have repeatedly been observed in which renal insufficiency followed administration of sulfonamides and necropsy disclosed no evidence of obstructive crystallization. The writer has seen several such cases. In 2 patients with anuria due to sulfathiazole, Prien[18] took renal biopsies during decapsulation with precautions to prevent solution of crystals but found none of the latter; there was focal necrosis of the tubules. In these cases the necropsy reveals only regressive changes in the tubular epithelia which go on to more or less widespread necrosis. Both the proximal and distal segments of the nephron may be implicated In 12 cases studied by Bergstrand[19] predominantly the [illegible] affected; the picture resembled that [illegible]

prepared [illegible] demonstrable There is intertubular edema and [illegible] varying degree Minute granulomata composed largely of plasma cells and eosin [illegible] cells, may be seen (*cf.* [illegible] [illegible]ally show little change.

catheterization, but renal insufficiency nevertheless [illegible] termination Necropsy disclosed tubular necrosis but no intratubular obstruction by crystals In some cases of this type in which renal colic, gross hematuria and the presence of sulfonamide crystals in the freshly [illegible] of damage by sulfonamide

The *clinical picture* of sulfonamide nephrosis is akin to that of other forms of necrotizing nephrosis (p 410) There is oliguria, which may go

festations of crystalluria are absent and which set in insidiously with oliguria, only when the patient becomes nauseated, somnolent, disoriented or very weak despite disappearance of fever may suspicion be aroused that there is trouble other than that due to the original infection. When sulfonamide nephrosis produces severe oliguria the mortality is high, although the writer is not acquainted with large statistics

The *treatment* is that of acute renal insufficiency (p. 223). Even though there are no obvious symptoms of crystalluria, all patients should be cystoscoped, the ureters catheterized and the renal pelves irrigated with warm 2.5 per cent sodium bicarbonate solution. An attempt should be made to alkalinize the urine by oral administration of sodium bicarbonate or intravenous injection of sodium bicarbonate or Hartman's solution. Overly enthusiastic administration of sodium salts, which may lead to heart failure, should be guarded against. Actually, there is no evidence that alkalinization in any way helps in sulfonamide nephrosis; it is attempted in the absence of ureteral obstruction only because of the possibility that there may be intratubular obstruction by crystalline aggregates. Rapid improvement has been observed to follow renal decapsulation (*cf.* Prien[49]), but the operation has failed in other cases (2 seen by the writer many years ago) and its value is not proved.

Other Chemical Nephroses.—In addition to mercuric chloride, carbon tetrachloride and the sulfonamides, many other chemicals produce necrotizing nephrosis. Among them are ethylene glycol (antifreeze, *cf.* Allen[54]), diethylene glycol (the poisonous constituent of the elixir of sulfanilamide which caused many deaths in 1937), tartrates, chromates, borates, bismuth salts, oxalic acid, sulfuric acid, hydrochloric acid, arsphenamine and many others. Many fatal cases of necrotizing nephrosis have been due to industrial or suicidal poisoning by these chemicals. Experimentally, uranium nitrate has been extensively used for the production of renal damage; both tubular necrosis and glomerular lesions result (*cf.* MacNider[55] and, for a general review of experimental nephropathies, Horn[56]).

NECROTIZING NEPHROSIS DUE TO TRAUMATIC SHOCK (THE CRUSH SYNDROME)

It has long been known that oliguria is part of the clinical picture of shock. That this oliguria is due to renal insufficiency was shown during World War I by observations that urea excretion in the urine is low (Richet and Flamant[57]) despite the presence of azotemia (Duval and Grigaut[58]). In many patients in shock, renal insufficiency contributes significantly to the symptomatology and to the fatal outcome. As a rule, renal function improves as shock clears. But exceptionally such is not the case, after disappearance of shock, impairment of kidney function persists and may go on to fatal uremia. Bywaters and Beall[1] observed in victims of crushing injuries during the bombardment of London that following recovery from shock the renal insufficiency may persist and some of the patients succumb to uremia even though the manifestations of shock have disappeared and the blood pressure risen to hypertensive levels. Similar observations had been made in World War I (Minami[59]) and in civilian accidents (Husfeldt and Bjering[60]) But they attracted little attention and the interest of the profession in the remarkable persistence of renal insufficiency *after* recovery from shock resulted from the work of Bywaters and Beall. Because most of their first patients had been crushed beneath fallen masonry or other heavy material, they coined the designation *crush syndrome*. However, post-traumatic uremia follows not only crushing injuries but also battle

In ... clinically demonstrable ... proportion of the cases. In fact, ... h is doubtless the reason that so little was known of the "crush syndrome" prior to World War II. Quite the opposite holds in war. Mallory[61] found the lesion in 18.6 per ... battle casualties in Army hospitals in ...

has generally been ... Whether lesser degrees of ...

Pathological Anatomy.—The kidneys are usually enlarged ...

... the cut section is usually moist and ... the edge of the capsule. The cortex is usually pale and the ...

seen in the sections as eosinophilic precipitates of different size and ... The blood content of the loops varies, sometimes ischemia is indicated by a paucity of red cells in the capillaries but in other cases they are well ... , but there may ...

... increased granularity of the ... ome.

... *in the tubules.* The epithelial cells are ...

... segments of the tubule are ... change. Areas of tubular

collapse are common. The necrotic tubule may undergo localized dilatation (herniation) or may rupture with extrusion of a cast or other content. Such rupture was beautifully demonstrated by Oliver[64] by microdissection Dunn[3] observed that the necrotic segments are not rarely in apposition to veins, through the thin walls of which they may rupture and produce thrombosis. While all divisions of the tubule may be affected, Bywaters and Dible and Lucké pointed out that the ascending limb of Henle's loop and the distal convoluted tubule are generally most severely affected. It was this observation that led Lucké to coin the designation low nephron nephrosis, of which the crush syndrome is the paradigm. However, it is to be emphasized that while the distal portions of the nephron are usually the most severely affected, the proximal convoluted tubule is also implicated and may be the seat of widespread necrosis.

Regeneration of the tubular epithelum starts within a remarkably short time and is often definite in cases which succumb in the second half of the first week. The newly formed cells are flat elements which then become more cuboidal. Lucké found that within ten days most of the damaged tubules are completely relined. Regeneration thus becomes pronounced at about the time that diuresis is apt to set in, if it does so at all.

Often the feature that first strikes the eye on looking at the section through the low power is the filling of the tubular lumens by casts and débris. In the upper parts of the nephron, the tubular lumens contain precipitated protein identical with that in Bowman's space and débris of necrotic and desquamated tubular cells. These may be agglomerated into dense hyalin, granular or epithelial casts. Much more characteristic, however, when present, are the pigmented casts which occur in the more distal divisions of the nephron—the ascending limb of Henle's loop and the distal convoluted and collecting tubules. They are brown in unstained preparations and usually cooper-colored in hematoxylin-eosin sections. Bywaters *et al.*[65] showed that these pigmented casts do not stain positively for free iron but that their tinctorial and spectroscopic reactions reveal heme pigment. *Since the urine contains myoglobin, it may be accepted* that the heme pigment is myoglobin, although the appearance and staining reactions are the same as those of hemoglobin casts Heme casts are absent in some instances of crush syndrome and in others they are scanty. Lucké found them only infrequently when survival was less than two days. However, in other cases they are numerous and may be especially prominent in cross-sections of the papillæ where massive granular or homogeneous brown casts may block most of the collecting tubules.

In the later stages, there exceptionally occurs dense leukocytic invasion of the tubules with an appearance like that of ascending pyelonephritis (Bywaters and Dible).

Surrounding the necrotic tubules are often foci of edema and infiltration with lymphocytes and histiocytes By the end of the first week fibroblastic activity may be evident and replacement of destroyed tubules by young scar tissue may already have started (Bywaters and Dible, Lucké). Whether chronic renal disease ever takes origin in such a process is, so far as I am aware, not known.

Pathogenesis.—Clinical observation differentiates two stages of the crush syndrome:

1. *Impaired Glomerular Filtra*
but no hyposthenuria. In fact the [illegible] a specific gravity exceeding 1.025 and a urea content of over 3 per cent. These findings indicate that in this initial stage the impairment of renal [illegible] of glomerular filtration and tubular
[illegible]

kidney and perhaps [illegible] filtration. That renal [illegible] in shock proportionall[illegible] by clearance methods [illegible] present at this stage [illegible] discussed in more detail above (p. 72).

2. *Impaired Tubular Function.*—If improvement does not occur, the [illegible] small volume of urine [illegible] lar function [illegible] tomical ex-

[illegible]

tional capacity, so that polyuria and hyposthenuria are present and the patient may suffer from or even succumb to salt and water depletion.

Anatomically, in 260 battle injuries, Mallory found that oliguria and nitrogen retention precede the first recognizable morphologic changes. These appear about eighteen hours after injury and consist in lipid vacuolization of the ascending limb of Henle's loop. Only from the third day on did Mallory find tubular necrosis

The beautiful experiments of Van Slyke and his coworkers[47] point in the same direction [illegible] and traumatic [illegible] (p 38) They f[illegible] blood flow has fallen below 5 per cent of normal. So low a renal blood flow was attained in these experiments only after the hemorrhagic or traumatic shock had been maintained for several hours Van Slyke and

[illegible]

period of complete ischemia results in irreversible renal damage with death from uremia in four to eight days.

The evidence is very strong that the primary cause of damage to the tubular epithelia in the necrotizing nephrosis of traumatic shock is impairment of nutrition by decreased renal blood flow. In his careful study of 260 battle injuries, Mallory showed a close parallelism between depth of

shock and renal involvement. The clearance measurements of Lauson *et al.* (p. 78) indicate a profound fall in renal blood flow in hemorrhagic and traumatic shock. In these forms of shock in dogs, Van Slyke found that the functional accomplishment of the tubular epithelia, measured by the PAH extraction (p. 38), is reduced only when renal blood flow is reduced to less than 5 per cent of the normal value. He also showed that clamping of the renal artery for two hours is followed by a protracted period during which functional depression of the tubule cells is documented by diminished PAH extraction; as mentioned above, if the artery was occluded for four hours the damage was irreversible and the animal succumbed to uremia in four to eight days as in human post-traumatic anuria.

Of the primacy of decreased renal blood flow in the necrotizing nephrosis of traumatic shock, there would thus seem to be little doubt. But accessory factors may also be significant. Of these the most important in cases with extensive damage to muscle seems to be the pressence in the glomerular filtrate of myoglobin liberated from traumatized muscle. It was mentioned above that Bywaters and his associates showed that the heme pigment eliminated in the urine in the crush syndrome is myoglobin. Since myoglobin has a molecular weight (17,000) much smaller than that of hemoglobin (68,000), it passes through the glomerular filter much more rapidly than hemoglobin— according to Yuile and Clarke[68] about 25 times as fast. How heme pigments in the glomerular filtrate may damage the renal tubules will be discussed in more detail in connection with post-transfusion nephrosis (p. 433). Here it may be mentioned that such injury may result from plugging of tubules by heme casts or by cytotoxic action of heme derivatives entering the cells. Blockage of tubules by myoglobin casts can at most be only an accessory factor because in some cases it is absent and in others only a small fraction of the nephrons is affected. It is likely that myoglobin derivatives in the glomerular filtrate can exert a toxic action on the tubule cells. In rats in which one hind limb was crushed, Corcoran and Page[69] found that those which were injected with myoglobin had much more severe degenerative changes in the tubules and more extensive formation of pigment casts than those which were given an equal volume of salt solution That heme derivatives should exert cytotoxic action more readily on tubular cells with nutrition already impaired by ischemia would appear plausible. It is, indeed, also possible that formation of pigment casts is favored by previous ischemic damage to the tubular cells, akin to the predisposition to thrombosis by damage to the vessel wall. That nephrotoxic substances are formed in traumatized tissues has been suggested, but is not supported by convincing evidence

Clinical Picture.—In civilian life clinically demonstrable necrotizing nephrosis follows traumatic shock in only an extremely small proportion of the cases. In fact, the sequence is distinctly a rarity, which is doubtless the reason that so little was known of the "crush syndrome" prior to World War II. Most of the few cases in large cities follow automobile accidents. How frequently, on the contrary, the crush syndrome follows battle casualties is shown by Mallory's finding of the lesion in 18 6 per cent of 427 unselected autopsies on battle casualties in Army hospitals in Italy. Perhaps the main reason for the difference is that in civilian life in recent

recent years the period of shock following trauma has been greatly abbreviated by prompt administration of blood or plasma and other treatment. Whether lesser degrees of renal damage, quickly reversed with amelioration of shock, *follow civilian* trauma with greater frequency remains to be studied, but seems very probable in the light of the almost invariable oliguria in shock.

Because of the constancy of oliguria in shock, the onset of necrotizing nephrosis due to traumatic or surgical shock is rarely suspected in its early stages in civilian practice. On very rare occasions, on surgical services, detection of a s [illegible] brown or red urine, which proves to be due to heme pigment (myog[illegible] sion of severe i[illegible] when the patient comes out of [illegible] of blood pressure to normal values or above. Or search for the cause of apathy, restlessness, nausea or vomiting reveals azotemia. The oliguria persists or goes on to anuria Correspondingly, the nonprotein nitrogen of the blood rises Despite the mounting azotemia, for several days the patient may have no symptoms other than those attributable to the injury or may feel well This latent period of several days of relative well-being often renders it difficult for the relatives of the patient to appreciate the gravity of the situation. In other cases, apathy, *mental torpor or disorientation*, or nausea and vomiting appear early and the symptoms of the initial trauma and those due to renal insufficiency merge with one another. In some cases, the patient does not come out of the causative shock, which persists with hypotension, and renal insufficiency is only one of the factors producing the lethal outcome In others, though the cerebral and gastrointestinal symptoms are unremitting from the onset, the recovery from shock is evidenced by rise in blood pressure to hypertensive levels and a warm skin

Oliguria is constant In cases seen at the start the specific gravity is high, over 1 020 After a day or two the specific gravity falls and is most often around 1 010 despite a urinary volume which may be less than 100 cc In the first days the urine is usually cloudy because of the presence of débris. In the cases due to muscle trauma the urine is smoky, dirty brown or reddish The discoloration is due to myoglobin, for the sediment rarely reveals many red blood cells Bywaters pointed out that the pigment granules and casts may sediment out so completely that the supernatant

thenuria the pH rises There is almost always considerable proteinuria due to serum proteins and the urine may boil solid With hyposthenuria the urea concentration in the urine is low despite azotemia. Bywaters states *that in the* crush syndrome the chloride content of the urine tends to be high notwithstanding a low plasma chloride level—like the low concentration of urea an indication of severe tubular damage with diminished ability

to change the composition of the glomerular filtrate in accord with the needs of the organism.

The sediment is usually abundant at the start. There may be various types of casts and much epithelial débris. Red cells are rarely numerous and may be very few. The most striking sediment is found in the early days of the crush syndrome. It is brown or reddish-brown in color and microscopically is seen to contain pigmented casts and granules of myoglobin. Casts of various morphologies are seen as a result of conglutination of pigment granules, epithelial cells or their débris, and hyaline substance. The pigment granules should not be confused with erythrocytes; they disappear after the first days.

As a result of the renal insufficiency, azotemia develops and the non-protein nitrogen of the blood may reach exorbitant heights. The changes in blood chemistry common to all varieties of uremia (p. 57) occur. These may be altered by special circumstances such as depletion of electrolytes by vomiting or unusual augmentation of the potassium content of the plasma when there is extensive breakdown of muscle; according to Bywaters, the concentration of potassium in affected muscle falls to less than one-quarter of its normal value in the crush syndrome. Renal acidosis is present, at the start it may be augmented by lactic and other acids from the traumatized tissues. In the early stages the hemoconcentration correlated with the causative shock is revealed by a high hematocrit reading.

At the onset the blood pressure is generally low, although exceptionally vasoconstriction fully compensates for oliguria and the arterial tension is maintained. After the shock has passed away the blood pressure rises and moderate hypertension is the rule. Usually this does not exceed 160/100 mm., a considerable hypertension in the face of the debilitated general condition and electrolyte depletion and oligemia that frequently develop. Exceptionally, the blood pressure rises as high as 200/110 mm Edema is absent unless it is produced by excessive administration of fluid. I have not seen retinal lesions from the hypertension.

If the oliguria persists or goes on to anuria, uremic symptoms (Chapter 7) appear within a few days. Not rarely, azotemia and uremia progress despite increase in urinary volume to such polyuric levels as 3000 or more cc. daily. In these cases the urine is so dilute that renal insufficiency exists despite the large urinary volume A fatal outcome, sometimes from electrolyte depletion, may then dash the hopes awakened by the polyuria.

The *prognosis* is serious in all cases in which the clinical picture definitely indicates necrotizing nephrosis The prognosis was especially grave in the crush syndrome during World War II and in battle wounds About two-thirds of Bywaters' cases of crush syndrome succumbed in the first week. Lucké estimated the mortality rate in definitely established lower nephron nephrosis at over 90 per cent. In necrotizing nephrosis in civilian life the mortality is not nearly as great, in my experience less than 50 per cent. This is probably largely due to improvement in management of fluid and electrolyte balance. Death often occurs suddenly toward the end of the first week. In some instances of crush syndrome in which this occurred after cardiac irregularity, Bywaters found the electrocardiographic changes

of hyperpotassemia (p 211), the cardiac effect of which is *perhaps the* ir [illegible] If the patient survives the first w [illegible]

and the p[illegible]

When the patient recovers from necrotizing [illegible] etiology, complete recovery of renal function is usually slow despite the fact that the patient feels entirely well. It is generally months before hyposthenuria disappears. By measuring urea, inulin and PAH clearances, Finkenstaedt *et al.*[79] demonstrated persistence of impairment of renal function for as long as four and a half years after acute renal failure. I have seen no cases of chronic renal disease which demonstrably took origin in *necrotizing nephrosis*, but in view of the frequently protracted impairment of renal function the possibility of such a course of events merits study

The treatment is discussed in Chapter 7

HEMOGLOBINURIC NEPHROSIS

A dreaded result of transfusion of incompatible blood is acute renal insufficiency. Since necropsy in the high proportion of cases which are fatal reveals necrotizing nephrosis, and hemoglobinuria* plays a fundamental rôle in the pathogenesis, the designation *hemoglobinuric nephrosis* [illegible] may be between major blood groups

[illegible]

the incidence of hemolytic reactions was 1 8 and the mortality [illegible] t[illegible] (Ell[illegible] and DeBakey[77]) Most of these fatalities due to in-[illegible]

[illegible] molecular weight as serum albumin

[illegible]

of that of creatinin, which is interpreted as [illegible]

[illegible]

dog can reabsorb by athrocytosis between 2 and 3 mg of hemoglobin per minute. This amount is less after hemoglobinuria persists or is soon repeated, with corresponding depression of the renal threshold for hemoglobin, presumably because of decreased

substrate of acute renal insufficiency in this country; in countries where blackwater fever is prevelant, it has probably always been the leading cause of acute uremia through the intermediacy of hemoglobinuric nephrosis.

Among the other circumstances in which intravascular hemolysis may lead to hemoglobinuric nephrosis are: burns, sulfonamide reactions; potassium chlorate, arsine and other forms of chemical poisoning, intoxication by plasmoquine and quinine (taken as an abortifacient); mushroom poisoning; favism; eclampsia gravidarum; and the intravenous injection of distilled water or hemolysis by hypotonic irrigating fluid during transuretheral resection. On the other hand, Burwell *et al.*[78] state that hemoglobinuric nephrosis is rare or has not been observed in the following hemolytic syndromes: paroxysmal cold hemoglobinuria, paroxysmal nocturnal hemoglobinuria, cold hemoglobinuria due to a high titer of cold agglutinins, and hemolysis of the recipient's cells due to a high titer of isoagglutinins in Group O blood from a universal donor. Nor does it occur in march hemoglobinuria or in familial or acquired hemolytic icterus, even during crises, or in acute hemolytic anemias. The reason may be that in these forms of hemolysis the hemoglobin concentration in the plasma does not rise sufficiently high.

Pathological Anatomy.—The kidneys are enlarged and may weigh over 500 grams. The capsule is not adherent. The surface and cut section of the cortex are pale gray or mottled and moist. The Malpighian bodies are not prominent. The medulla is dusky and sometimes brownish; radial brown streaks may be seen.

The histological picture is dominated by regressive changes in the tubular epithelia culminating in necrosis, and by pigmented casts in the lower nephron.

The glomeruli show little change. There may be protein in Bowman's spaces, some of which may be dilated.

Most striking, when numerous, are brick-red or brown granules, masses or well formed casts in the lower nephron from the ascending limb of Henle's loop to the collecting tubules. The distal segments of many nephrons may be completely occluded by the pigmented masses; especially the collecting tubules are apt to be so tightly packed that the lining epithelium appears to be compressed In some cases the casts are numerous, in others they are seen in only a small proportion of the tubules. The pigmenta[illegible] tion. [illegible] teased [illegible] by Harrison *et al.*[79] proved to be pigmented by methemoglobin and not hematin. Heme casts in the lower nephron have been observed as early as one and a half hours after intravenous injection of hemoglobin into dogs (Harrison) and two hours after a hemolytic reaction in man (Ayer and Gauld[80]). In addition to the casts of heme pigment, casts of eosinophilic material, desquamated epithelial cells and cellular débris are found in all segments of the tubule

The tubular epithelia exhibit regressive changes of various degrees. Ayer and Gauld observed cloudy swelling and eosinophilic casts in the proximal convoluted tubule as early as three hours after a hemolytic

reaction. Droplets of hemoglobin derivatives—having the same color and staining reactions as the pigment in the lumens—may be discernible in ... proximal and distal tubules. Hemosiderin,

cated. Lucké[2] includes hemoglobinuric nephrosis in his concept of ... nephron nephrosis. It is true that the pigmented casts are found only in ... of the nephron, but the regressive changes may also ... Bell's[81] ... Dilated

tubules are often seen; whether these are proximal to obstruction by casts remains to be determined. Within a few days *regeneration* of the tubular epithelium is evident. Individual calcified tubules are sometimes seen in the later stages. There are varying degrees of intertubular edema and cellular infiltration

The *complete functional recovery* in cases that survive indicates that tubular regeneration leads to quite complete healing. However, in a patient who succumbed to homologous serum hepatitis three months after recovery from severe hemoglobinuric nephrosis, Burwell *et al.* found

and experimental investigation since Ponfick[82] first attempted to reproduce *the changes of blackwater fever by injecting heterologous blood into* animals and observed pigmented casts in the tubules Subsequent investigators of blackwater fever, notably Yorke and Nauss,[83] attributed the urinary suppression to mechanical plugging of the tubules by hemoglobin casts On the basis of injection of hemoglobin solutions into rabbits and *in vitro* studies of the precipitation of hemoglobin, Baker and Dodds[84] concluded that hemoglobin is precipitated in the tubules only when the urine is acid and has a fairly high concentration of electrolytes. These are conditions which are first attained when the urine reaches the lower

ments accord with clinical observations, *for heme casts are found only in* the lower nephron, where the urine is acidified and concentrated. However, other observers obtained different results De Novasquez[85] and Yuile *et al.* were unable to confirm the results of Baker and Dodds in rabbits. Bing[87]

injected as *much as* 33 cc of packed red cells laked with distilled water into humans, which produced marked hemoglobinuria, but there was no

renal damage. Gilligan and his associates produced pronounced hemoglobinuria by injection of as much as 16.4 Gm. of stroma-free hemoglobin into humans without inducing more than transitory proteinuria.

It would thus appear that the occurrence of marked hemoglobinuria *per se* does not suffice to produce hemoglobinuric nephrosis. Other conditions must also be present. Light was cast on these by the experiments of Yuile and his coworkers. They first showed that in normal rabbits injection of relatively pure hemoglobin solutions did not damage the kidneys. But when the hemoglobin solutions were injected after the kidneys had been damaged by preliminary clamping of the renal artery for fifteen or twenty-five minutes or injection of sodium tartrate renal lesions were produced which closely simulated those of human hemoglobinuric nephrosis with regressive changes in the tubular epithelium and heme pigment casts. They found that the renal damage was the more pronounced the greater the preliminary tubular injury, the higher the hemoglobinemia, and the more acid the urine. Flink[89] also found a correlation between the height of the hemoglobinemia and the severity of the renal damage in dogs Hamilton *et al.*[90] observed transitory depression of urea clearance after infusion of a 7 per cent hemoglobin solution into dogs; this did not occur with plasma.

Quite probably, a similar constellation of pathogenetic factors operates in clinical hemoglobinuric nephrosis. Transfusions are often given to

[illegible]

eral circulatory failure. During the reaction produced by transfusion of incompatible blood, there may also be renal arteriolar constriction and consequent ischemia; Mason and Mann[91] and Hesse and Filatov[92] found that intravenous injection of hemoglobin solution is followed by decrease in the volume of the kidney. It is true that Harrison *et al.* found normal renal blood flow in 2 dogs following injection of methemoglobin in amounts sufficient to produce renal damage, but the measurements may not have coincided with the period of shock, which is often very transitory. The observations of Miller and McDonald,[93] to be mentioned below, show that in man the injection of hemoglobin solutions can produce renal vasoconstriction. Clinical observation (*cf.* Bordley[94]) indicates that the more incompatible blood infused, the more severe is apt to be the renal damage,

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favors the formation of heme casts after injection of hemoglobin were mentioned above, more recent, and carefully controlled, studies by Yuile indicate that after injection of hemoglobin solutions into rabbits, both heme cast formation and renal functional disturbances are more severe with acid urine The urinary volume may also be an important conditioning factor. Harrison found that much lower plasma methemoglobin levels produce renal damage when there is oliguria.

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an important and perhaps an initiating and predominant factor. The epithelial necrosis does not result from obstruction of the tubules from heme casts (apart from perhaps the segments in which the tubules are

iron It is conceivable, though unproved, that when large amounts of some heme derivatives are taken up by the tubular cells or formed in them, they may be cytotoxic, especially if the nutrition of the cell is previously impaired by ischemia Harrison *et al* believe that hemoglobin oxidized to methemoglobin in the tubular fluid may act as an oxidant and exert its cytotoxic action through catalysis of the oxidation of sulfhydryl groups; they state that there is evidence that the tubular cells are highly susceptible to agents which combine with or oxidize sulfhydryl groups

The relative importance of occluding heme casts and necrosis of the tubular epithelium in the renal insufficiency of hemoglobinuric nephrosis probably varies from case to case and at different stages of the process. At most necropsies the proportion of nephrons blocked by casts is so small that this can hardly be the predominant factor in producing renal insufficiency through the intermediacy of internal hydronephrosis * In only 2 of 9 patients succumbing to hemoglobinuric nephrosis did deGowin regard the proportion of tubules blocked by casts as having been enough to constitute a serious factor in the renal failure. Tubular epithelial damage appears to be at least most often the predominant element in producing

Clinical Picture.—When hemoglobinuric nephrosis results from transfusion of incompatible blood, it generally follows an immediate reaction during the transfusion, which may have occasioned cessation of the latter. Exceptionally, the immediate reaction is not evident or is unrecognizably intermingled with the symptoms of the condition for which the transfusion is being given The immediate reaction is more apt to be overlooked when the blood is given to an anesthetized subject; this happened in a recent case (fatal in eleven days) in which it was thought that mental confusion was due to slow recovery from the anesthetic until jaundice appeared seventeen hours later and hemoglobinuria was looked for and found. When the immediate reaction is not observed, hemoglobinuria and oliguria call attention to the danger. The immediate reaction consists in such

* Harrison *et al* point to the possibility that increased viscosity of the tubular contents in hemoglobinuria may be concerned in obstructing the flow of urine

renal damage. Gilligan and his associates produced pronounced hemoglobinuria by injection of as much as 16.4 Gm. of stroma-free hemoglobin into humans without inducing more than transitory proteinuria.

It would thus appear that the occurrence of marked hemoglobinuria *per se* does not suffice to produce hemoglobinuric nephrosis. Other conditions must also be present. Light was cast on these by the experiments of Yuile and his coworkers. They first showed that in normal rabbits injection of relatively pure hemoglobin solutions did not damage the kidneys. But when the hemoglobin solutions were injected after the kidneys had been damaged by preliminary clamping of the renal artery for fifteen or twenty-five minutes or injection of sodium tartrate renal lesions were produced which closely simulated those of human hemoglobinuric nephrosis with regressive changes in the tubular epithelium and heme pigment casts. They found that the renal damage was the more pronounced the greater the preliminary tubular injury, the higher the hemoglobinemia, and the more acid the urine. Flink[89] also found a correlation between the height of the hemoglobinemia and the severity of the renal damage in dogs Hamilton *et al.*[90] observed transitory depression of urea clearance after infusion of a 7 per cent hemoglobin solution into dogs; this did not occur with plasma.

Quite probably, a similar constellation of pathogenetic factors operates in clinical hemoglobinuric nephrosis. Transfusions are often given to patients in more or less shock who consequently have decreased renal blood flow (p. 81). The writer does not recall seeing hemoglobinuric nephrosis follow a transfusion in a patient without some evidence of peripheral circulatory failure. During the reaction produced by transfusion of incompatible blood, there may also be renal arteriolar constriction and consequent ischemia. Mason and Mann[91] and Hesse and Filatov[92] found that intravenous injection of hemoglobin solution is followed by decrease in the volume of the kidney. It is true that Harrison *et al* found normal renal blood flow in 2 dogs following injection of methemoglobin in amounts sufficient to produce renal damage, but the measurements may not have coincided with the period of shock, which is often very transitory. The observations of Miller and McDonald,[93] to be mentioned below, show that in man the injection of hemoglobin solutions can produce renal vasoconstriction. Clinical observation (*cf.* Bordley[94]) indicates that the more incompatible blood infused, the more severe is apt to be the renal damage,

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reveals necrotizing nephrosis The glomeruli show little change. The ... In 4 instances of pyloric

tubule, the resemblance to the crush syn... the presence of numerous herniations of necrotic tubules into veins (p. 426). ... vomiting with resultant alkalosis, there is

off the pylorus The mechanism of the ... primarily decreased renal blood flow with consequent ischemic damage to the tubular epithelia, the decreased renal blood flow is a result of electrolyte depletion and consequent diminution in blood volume. Since the nature ... disturbances caused by immoderate vomiting and

become far rarer than it was two decades ago

CHOLEMIC NEPHROSIS (THE HEPATO-RENAL SYNDROME)

Not very rarely, when convalescence seems smoothly initiated following an operation on the gall bladder or common duct, after an interval of one to six or even more days, malaise develops, the temperature rises, oliguria sets in and may go on to anuria, the patient becomes restless and then perhaps delirious or comatose, and in a considerable proportion of the cases succumbs with the clinical picture of uremia. At first the urine is of high specific gravity, but

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of leptospiral infections and causes most of the deaths is a necrotizing nephrosis (cf Stiles *et al* [99]) A similar picture has been observed following traumatic pulpification of the liver (Schutz *et al.*[100]). In dogs, Helwig and Schutz[101] described renal insufficiency and degenerative changes in the tubular epithelium following experimental pulpification or ischemic necrosis of the liver

Anatomically, in the early stages, the kidneys may reveal only modest regressive changes in the tubular epithelium This was true in a case at Mount Sinai Hospital reported by Garlock and Klein[102] which did not succumb until the twelfth day Most often, however, severe regressive changes going on to focal necrosis of the tubular cells soon appear, with little change in the glomeruli The tubular epithelium contains granules of bile pigment (according to Allen[103] this involves only the proximal nephron down to Henle's loop) and there are bile stained casts in the lower

manifestations as restlessness, weakness, confusion, sweating, chills, high fever, vomiting, pains in the back, tingling, thoracic oppression, cyanosis, dyspnea, fall in blood pressure, collapse, and urticaria. These immediate symptoms, apart from very rare instances of quick death, generally subside within a matter of hours. Not every patient who has such an immediate reaction and recovers, develops clinically evident hemoglobinuric nephrosis. Especially if the reaction is quickly detected and the transfusion stopped before much blood is given, urinary suppression is unlikely. While severe hemoglobinuric nephrosis has been observed with transfusion of less than 100 cc. of incompatible blood, the incidence increases with the size of the transfusion. Jaundice appears in a high proportion of the patients who are to develop urinary suppression, but not in all.

After subsidence of the immediate reaction, the patient may feel de- [illegible]

or methemoglobin and heme-pigmented granules and casts are present. These quickly lessen and disappear in a few days, as a result of clearing of the hemoglobinemia, which occurs rapidly. The specific gravity of the small amount of urine passed is fixed in the vicinity of 1.010 and the urea concentration is low. Correspondingly, there is mounting azotemia. The clinical picture of acute renal insufficiency (Chapter 7) develops. The blood pressure generally, though not always, rises, but marked hypertension is very rare. Retinal lesions are absent. Edema does not develop, other than terminal pulmonary edema, unless excessive fluids are forced or there is heart failure. At any time, no matter how desperate the situation and even after the patient is in uremic coma, the urinary volume may increase and rapid improvement set in. This may occur as late as the end of the second week. Goldring and Graef[95] observed advent of diuresis and recovery after sixteen days. Sometimes the onset of diuresis occurs too late to save the patient, who succumbs despite a urinary volume of over 3000 cc., which unfortunately is very dilute. The mortality is high. Formerly it was probably over 50 per cent of the cases in which the damage to renal function was severe enough to produce pronounced azotemia. But since fluid and electrolyte balance have been better controlled, the mortality has not been as high.

The treatment is discussed in Chapter 7.

NECROTIZING NEPHROSIS DUE TO VOMITING AND DIARRHEA

With severe vomiting, azotemia often develops. The same frequently occurs in the diarrheal diseases of infancy; it is rare, except in the tropics, in severe diarrhea in adults. According to the descriptions by Fraenkel and Simmonds[96] of the anatomical findings in the Hamburg cholera epidemic, severe necrotizing nephrosis is present in most fatal cases of cholera. In some instances of pyloric or intestinal obstruction, as well as in intractable vomiting in peritonitis, renal insufficiency dominates the clinical picture and the patient becomes uremic. In such cases necropsy

protein content of the urine. Circulatory disturbances may be concerned. Smith[108] and Bradley and h ... [109] showed that injection of a pyrogen, even if rise in tempe
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flow does not compensate for the diminished oxygen-carrying capacity of the blood Tubular reabsorption is an active process in which work is performed and consequently oxygen required On the other hand, Stieglitz[112] believes that the function of the tubular cells may be impaired by the siderosis which is constantly present That this is not the main cause is shown by the occurrence of hyposthenuria in secondary anemias where there is no siderosis and by the fact that the concentrating ability

very *evident at 30* per cent *One* often sees quick restoration of concentrating ability when the anemia is overcome by appropriate treatment Fouts and Helmer[113] found that the *induction* of a remission by liver treatment is accompanied by a rise in urea clearance.

nephron. The functional significance of the deposition of bile pigment is probably not great. Brown or green amorphous or crystalline spherules of underdetermined composition are often found in the tubules (Allen).

How the liver disease leads to the renal damage remains to be elucidated. As mentioned above, in cases succumbing early comparatively little morphological damage is seen in the kidneys; the necrotizing nephrosis develops later. The patients often display pronounced evidence of periph-

damage may underlie the hypovolemia and circulatory failure; Page's[104] finding that hepatectomized animals lose their vascular reactivity may be relevant in this connection. Such factors as surgical shock and vomiting undoubtedly often also contribute and may dominate. But in some instances of the "hepato-renal syndrome," these banal causes of renal failure do not seem to operate.

LARVAL NEPHROSES

Proteinuria may occur in the course of febrile diseases, afebrile toxemias, severe anemia, marked alkalosis or acidosis, and various other states in which there is reason to assume abnormalities in the composition of the blood. The proteinuria is usually slight and does not deplete the plasma proteins. Anatomical investigation in cases of this nature may show little that is definitely abnormal or there may be cloudy swelling, hyaline droplet degeneration or lipidal change in the epithelial cells of the kidneys. In addition to these regressive changes in the renal epithelium, there may also be storage in these cells of substances such as glycogen in diabetes mellitus and iron in pernicious anemia. These proteinurias document the mildest forms of nephrosis, for which reason they are here termed larval.

Febrile Proteinuria (Febrile Nephrosis).—The occurrence of proteinuria in fevers was first described by Solon,[105] and was termed febrile albuminuria by Gerhardt.[106] Proteinuria may occur in almost any febrile state, but is most common when the fever is very high and protracted.

Anatomically, cloudy swelling of the epithelium, particularly of the convoluted tubules, is found. Not uncommonly, there is also lipidal change of varying degree, though rarely marked. The proteinuria has generally been correlated with these changes in the tubules. It should be

about which we can tell little from the microscopic examination.

It would appear that pyrexia *per se* is one, though probably not the most important, factor in the causation of febrile proteinuria. This is indicated by the finding of Welty[107] that 77.5 per cent of 40 patients with healthy kidneys whose body temperature was elevated to between 105° and 106° F. for four to six hours by the Kettering hypertherm had an increase in the

Circulatory disturbances may be concerned.

a remarkable hyperemia of the kidney which is ... Such circulatory perturbations ... preceded by brief renal ischemia.

for similar renal lesions and proteinuria occur in various ... and chemical poisonings.

less than 0.1 per cent But there are unusual instances in which febrile proteinuria is of high degree, as much as 1 per cent of protein being present in the urine. Albumoses may accompany the albumin and have been observed even in the absence of the latter (Krehl and Matthes[110]). Small

ment, high specific gravity and low chloride content. Edema and hypertension are absent

The slight renal changes which result in febrile proteinuria exert no influence on the course of the primary disease They offer no diagnostic or prognostic aid and call for no modification in the dietetic or other treatment.

anemia, Christian[111] and Major long ago showed that when the patient is severely anemic there may be marked impairment of concentrating power. The defective renal function in this disease is probably due to poor oxygenation of the kidney cells by the anemic blood, the increase in renal blood flow does not compensate for the diminished oxygen-carrying capacity of the blood Tubular reabsorption is an active process in which work is performed and consequently oxygen required On the other hand, Stieglitz[112] believes that the function of the tubular cells may be impaired by the siderosis which is constantly present. That this is not the main cause is shown by the occurrence of hyposthenuria in secondary anemias where there is no siderosis and by the fact that the concentrating ability of the kidney is quickly affected by changes in the hemoglobin ...

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ADDENDUM: RENAL INVOLVEMENT IN MULTIPLE MYELOMA

A remarkable and specific renal lesion occurs in multiple myeloma. In fact, in somewhere between a half and a third of the cases renal insufficiency with consequent uremia is the dominant immediate cause of the fatal outcome (*cf.* Adams *et al.*[116]). Occasionally, myeloma is discovered in seeking for the cause of initially obscure renal insufficiency or proteinuria. In most instances, the only clinical manifestations of the specific renal lesions of multiple myeloma consist in proteinuria, hyposthenuria, azotemia and symptoms of uremia. Clearance studies by Armstrong[117] revealed that both glomerular filtration and tubular excretory capacity are impaired (blocking of a tubule would of course abolish filtration in the appertaining glomerulus). Edema is most often absent until the terminal stage, when it is difficult to separate the rôles of proteinuria and undernutrition in its production. Hypertension occurs in so small a proportion of these usually elderly patients that it may be coincidental: I do not recall hypertensive retinopathy or encephalopathy. Study of the urine in patients with azotemia reveals hyposthenuria. But the proteinuria is very variable in amount and composition. Either or both Bence-Jones proteins and serum albumin may be demonstrable by the usual clinical methods. Magnus-Levy,[118] who has studied the renal manifestations of multiple myeloma intensively, finds that massive proteinuria is largely due to Bence-Jones proteins. He states that Bence-Jones proteins have failed of detection because under certain conditons, especially when present in large quantity, they may be insoluble in boiling urine. In some cases which succumb to renal insufficiency nothing more than a faint trace of protein may be demonstrable in the urine during a period of observation of weeks or months. When urethane inhibits plasma cell growth, Bence-Jones proteins diminish in or disappear from the urine (Rundles *et al.*[119]). Armstrong found no relation between the proteinuria and the degree of renal damage.

The renal lesions of multiple myeloma are characterized by the presence of casts in the lower nephron and tubular atrophy terminating in disappearance of the nephron with replacement fibrosis. Grossly, the kidney is usually rather pale with a smooth surface. Most often it does not differ much from the usual size, but it may be a little enlarged or definitely contracted. Microscopically, in the cases which have succumbed with renal insufficiency, the most striking feature is usually the presence of great numbers of large, occlusive casts in the collecting tubules and sometimes the distal convoluted tubules, they may also be found in the loop of Henle The casts are dense and stain bright pink in hematoxylin-eosin preparations, they may be laminated. The casts are often surrounded by cells which have been regarded as foreign body giant cells, but that Allen[120] interprets as syncytia of fused tubular epithelia. Sometimes, masses of crystals are seen in the tubules. The crystals are doubtless Bence-Jones proteins and there is every reason to believe, though this has not been proved, that the casts contain these bodies. The tubules exhibit various stages of regressive change and atrophy going on to complete disappearance. The distegration of the tubular cells calls forth a highly cellular

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are ... of glomerular loops have been reported ... calcification of the tubules and casts may occur, doubtless a result of the osteolytic process

The evidence indicates strongly that the renal lesions of multiple myeloma result from obstruction of the tubules by casts. Thannhauser ... the first to realize that the renal lesions



FIG 13 —Section of kidney in multiple myeloma with Bence-Jones proteinuria. The tubules are obstructed by casts of Bence-Jones protein around which foreign body giant cells have formed

accord with the conception, although it has not been proved, that the casts take origin in the precipitation of Bence-Jones proteins in the distal tubule after the tubular fluid has been concentrated by reabsorption of water, alterations in the electrolyte constellation of the fluid occurring during tubular processing may also be concerned The Bence-Jones proteins(they apparently are multiple, all secreted by the myeloma cells) are of relatively small molecular size—molecular weight about 28,000—and pass through the glomerular filter into the tubular fluid It is to be presumed that up to a certain concentration the Bence-Jones proteins are reabsorbed by the tubular cells by athrocytosis (p. 130), but if the concentration is higher the proteins remain in the tubular fluid, either to be eliminated in the urine or precipitated as casts when enough water is

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reabsorbed. The results of injection of Bence-Jones proteins into animals have been conflicting; McMahon and Magnus-Levy[125] observed tubular

nephrosis. There seems no reason to believe that Bence-Jones proteins are specifically nephrotoxic; the renal damage results from obstruction of the tubules and perhaps—though this is purely hypothetical—from "choking" of

is fundamentally the same as that in other forms of renal damage. Often, deterioration is slow and an azotemic patient may get along for a year or two, usually with numerous transfusions. The anemia often dominates the symptomatology and presumably is due to both the bone marrow damage and the renal insufficiency.

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Chapter

16

CHRONIC NEPHROSIS

CHRONIC nephrosis* is characterized clinically by copious albuminuria and [illegible] changes in the proteins and lipids of the

[illegible]

symptomatology seems to consist almost purely in the consequences [illegible] hypalbuminemia due to massive albuminuria. Together with certain types of glomerulonephritis and doubtless diabetic glomerulosclerosis, chronic nephrosis constituted the chronic parenchymatous nephritis of older clinicians and the large white kidney of pathological anatomists.

What is here termed chronic nephrosis is widely known by Munk's[1] [illegible] that the

lipid in the [illegible] chronic nephrosis is used because it is noncommittal regarding the (still unknown) nature of the disease; it merely expresses the defining characteristics of the renal lesions, i. e., that they are chronic and non-inflammatory.

The separation of chronic nephrosis from glomerulonephritis and its recognition as a distinct clinical and anatomical entity was accomplished by several investigators in the [illegible] Munk[1] published a series of cas[illegible] were marked by edema, great [illegible] refractile lipoids in the urine, [illegible]

[illegible]

of the plasma, related the edema to the hypoproteinemia, and introduced the high protein diet

The introduction of the concept of chronic nephrosis as an entity distinct from glomerulonephritis inaugurated a controversy which has not yet fully subsided. Many cases with necropsy findings showing the absence of inflammatory lesions have been published. Nevertheless, unanimity of opinion as to the *nature* of the pathological process underlying the clinical manifestations and anatomical lesions has by no means been attained. Some investigators regard the disease as primarily acute glomerulonephritis which has healed so as to leave little or no evidence of the original inflammatory processes but only secondary degenerative changes. Others, and they are now in the decided majority, admit the primarily non-inflammatory nature of the lesions, but differ as to whether the condition starts as a



Fig. 14 —Kidney in chronic nephrosis occurring about six months after syphilitic infection Note the prominent radial striation of the cortex due to the light streaks of lipoid deposit (yellow in the specimen).

kidney disease or if it is not initially a disorder of metabolism, one of the results of whi
nephrosis is a
nephritis The evidence for this view is summarized below

THE PATHOLOGICAL ANATOMY OF CHRONIC NEPHROSIS

Chronic nephrosis has been regarded as a rare finding at necropsy; some physicians of large experience claim never to have witnessed an unequivocal case. Nevertheless, a considerable number of necropsies on

cases of chr
Murphy an
Mayer,[8] M
Ehrich,[13] 1
Blackman,
and others

nephrosis at autopsy. In recent years necropsies ...
... not succumb to renal insufficiency have become

The syphilitic cases have practically disappeared. ...
because of the persistent dogma that glomerular hyalinization in the absence of arteriolar sclerosis bespeaks glomerulonephritis, many cases of
chr ... and uremia are
dou ... much as was
for ... writer has no
do ...

... erately enlarged; the
... the smooth surface,
... egated here and there
...
broadened and clear
substance feels and
fatty change stand o...
nate with red areas.

Histologically, changes are seen in both the glomeruli and the tubules. In the type of case in which chronic nephrosis was first differentiated—*i. e.*, massive proteinuria and edema without renal insufficiency—the changes in the glomeruli are not conspicuous while there is very striking deposition of lipid in the tubular cells. Attention was thus focused on the tubules and the glomeruli were often reported as histologically normal; the process was sometimes spoken of as "tubular nephritis." Actually, the relatively inconspicuous changes in the glomeruli are doubtless of more importance
... probably
... at least
... further

have often been regarded as chronic glomerulonephritis and thus not included in the rubric of nephrosis.

The Glomeruli.—The Malpighian bodies were originally considered to show practically no morphological changes in chronic nephrosis. Later,

investigations of Bell[24] with the Mallory-Heidenhain azo-carmine stain, which brings out the basement membrane clearly. In the cases, mostly in children, which have a clinical picture of proteinuria and edema in the absence of hypertension and renal insufficiency, the glomerular changes are usually slight and may be hardly demonstrable. Most important is that the large majority of the glomerular capillaries remain widely patent. Such lesions as exist are degenerative; the endothelial and epithelial proliferation that constitutes the hallmark of glomerulonephritis is absent or minimal and focal. A varying portion of the glomeruli exhibits swelling and lipidosis of the walls of the loops and the visceral and parietal layers

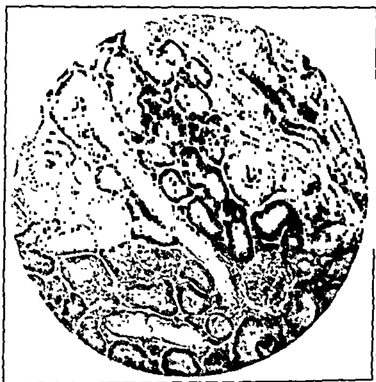


Fig. 15 —Frozen section of kidney in chronic nephrosis stained with Sudan and hematoxylin. The lipid in the tubular cells which has been stained by the Sudan appears black.

of Bowman's capsule Bell and Kantrowitz and Klemperer found the lipid deposited in the endothelial as well as the epithelial cells; the endothelial cells which contain lipid may be greatly swollen and more prominent than normally, thus simulating proliferation. The lipid deposited in the endothelial and epithelial cells of the glomeruli is partly doubly refractile and very small in amount compared to the amount of cholesterol esters in the tubular cells. Bowman's capsule usually contains coagulated protein Even in these cases without renal insufficiency or hypertension, there may be some degree of thickening of the basement membrane of the capillary loops. In other cases, as Bell[24] showed, the basement membranes are diffusely thickened to such an extent as notably to narrow the capillary

lumens.* The advance of this process leads to complete hyaline obliteration of the affected loops and the termination is the destruction of a varying proportion of the glomeruli. George Fahr[23] has published beautiful [illegible] of hypertension and renal insufficiency in chronic [illegible]

[illegible] of age 31 had diffuse and 3 focal thickening. [illegible] in these cases of chronic nephrosis with glomerular hyalinization closely simulates that of glomerulonephritis and they have doubtless generally [illegible] latter disease. The most important differential [illegible]

[illegible] In most instances these lesions are very well marked, but there are also cases in which the microscopic appearance is not that of a change of great severity. The proximal convoluted tubules are involved to the highest degree, the distal convoluted tubules and Henle's loops to a less extent, [illegible] the collecting tubules are but little affected Many of the tubules [illegible]

to fill the entire cell body with Sudan-staining substance and give it a vacuolated appearance in sections which have been passed through fat solvents Under the polarizing microscope, it is seen that most of the lipoids are doubly refractile (cholesterol esters). However, in the case of a child on the service of Dr Herman Schwarz in which hypercholesteremia was absent during life, anisotropic lipoids could not be demonstrated in the kidneys postmortem Such absence of doubly refractile lipoid in the tubular cells is apparently very exceptional, at least, I do not recall seeing or reading of any other instance of chronic nephrosis in which they were absent. Leiter[22] points out that the presence of anisotropic lipoids in the renal epithelia is very characteristic of the nephrotic syndrome, being rarely seen in other conditions, although isotropic fatty change occurs under a variety of circumstances There may be also considerable hyaline-droplet [illegible]

where they lie with casts, granular material and cellular detritus.

The degenerated tubular cells are replaced by regeneration Fahr[23] describes the process of regeneration as akin to that found in mercurial necrosis, starting with the formation of flat, almost endothelium-like cells under the degenerated elements.

* Because of the importance of the thickening of the capillary basement membrane, Bell speaks of these cases, here termed chronic nephrosis, as membranous glomerulonephritis

29

In the cases with extensive glomerular hyalinization and obliteration, there is tubular atrophy, which may be widespread. This is presumably secondary to the glomerular lesions; decreased blood supply and disuse may be concerned.

In cases of considerable standing there is irregular proliferation of interstitial connective tissue between the tubules. This is entirely a secondary change, apparently a reaction to the parenchymatous lesions and, where there has been tubular atrophy, a "replacement fibrosis" for destroyed tubules. The presence in the interstitium of nests and cords of cells laden with doubly refractile lipoid is very striking in some cases. In sections which have passed through alcohol, the lipoid has been dissolved out so that the cells have a clear cytoplasm like that of xanthoma



FIG 16 —Section of kidney in chronic nephrosis (same case as Fig 14) viewed through polarizing microscope with crossed Nicol prisms. Only the doubly refractile lipoid is visible, being brilliantly luminous in an otherwise dark field, it is present in large interstitial masses as well as in the tubular cells

cells ("pseudoxanthoma cells"). There can be little doubt that these are cells which have taken up the lipoid freed by the disintegration of degenerated epithelia. The origin of these lipoid-phagocytes is disputed. Some authors believe them to be phagocytic wandering cells, while others regard them as endothelial cells of lymph capillaries The frequently linear arrangement of the cells would seem to speak for the latter view.

The vessels of the kidney are usually unaffected. However, there may be atherosclerotic changes, as a part of the widespread atherosclerosis which Loewenthal[5] found in chronic nephrosis in young individuals. I have repeatedly seen atheroma much beyond the expected for the age at necropsy in nephrotic children, it is possible that it is correlated with the hypercholesteremia. Rarely, thrombi form over the atheromatous

. In a

areas,

boy, a

there was ... the latter of which produced hemiplegia ... cerebral arteries, fatal A nephrotic child with thrombosis of the aorta and another with an antemortem clot in the pulmonary artery were observed by Block *et al.*[21] Remarkably enough, they did not detect atheromatosis in these cases, so the arterial thrombosis may have been due solely to the changes in the blood

As the end stage of chronic nephrosis, Volhard and Fahr have described a *nephrotic contracted kidney* According to their description, the nephrotic contracted kidney is small and irregularly granular, the granules being yellow in color. Fahr and Munk originally believed that the contraction in these cases results only from primary tubular degeneration and atrophy. ... greater significance to the degenerative

can be present for a long time without the development ... kidney, for contraction was absent in Ehrich's[13] case of eighteen years' duration The least equivocal cases of nephrotic contracted kidney seem ... Shapiro[12] also published ... I have not seen any

THE ETIOLOGY OF CHRONIC NEPHROSES

Occurrence.—

sis The disease

some experienced ...

unequivocal example Many of the published cases are undoubtedly chronic glomerulonephritis Contrariwise, the general assumption that glomerular hyalinization is always due to either arteriolosclerosis or glomerulonephritis (in recent years diabetic glomerulosclerosis has also been recognized) has led to the diagnosis of some, perhaps many, instances of chronic nephrosis as glomerulonephritis Over a period of many years at Mount Sinai Hospital several cases of chronic nephrosis were seen annually Rosenberg[10] observed 39 examples of lipoid nephrosis among 429 "acute nephritides," i e, about 10 per cent In the opinion of the writer, chronic nephrosis is not as rare among adults, especially after the age of fifty, as has generally been thought Many, if not most, of the instances in which a nephrotic syndrome sets in insidiously in the elderly, are cases of chronic nephrosis and not glomerulonephritis, they have been regarded as the latter because glomerular hyalinization is found at necropsy Chronic nephrosis is not rare in children, especially under the age of five; I see many cases annually in private practice Large series of pediatric cases were long ago published by Holt and Howland,[6] Marriott,[21] Clausen,[22] Schwarz and Kohn,[23] and Wolbach and Blackfan [24] Some of these cases doubtless

were chronic glomerulonephritis in the nephrotic phase, but others were chronic nephrosis. In 6 necropsies on young children with a nephrotic syndrome, Heyman and Startzman[34] found 3 without any inflammatory lesions in the kidney; in the other 3 the inflammatory changes were interstitial and pyelonephritic.

Age Incidence and Predisposing Factors.—Chronic nephrosis is seen most often in childhood, especially before the age of five years. However, cases are also seen in all subsequent decades. As mentioned above, the writer believes that many nephrotic syndromes in the elderly are actually due to chronic nephrosis and not glomerulonephritis, as they have been almost universally regarded.

Apart from youth, little or nothing is known of any factors predisposing to chronic nephrosis. Knauer[35] believes that the disease occurs predominantly in pasty children with evidence of the exudative diathesis. Volhard,[36] who observed cases in two brothers, thinks that there may be a familial predisposition. This author also saw several cases that followed working in the wet. There has been no evidence of the significance of any of these factors in my experience

Causation.—Some cases of chronic nephrosis are manifestly the result of an infection. In others—in my experience by far the larger part—the etiology remains entirely in the dark, for which reason they have been termed genuine or cryptogenic nephroses. Older etiologic statistics are typified by Rosenberg's 39 cases of chronic nephrosis, of which 16 were syphilitic, 7 followed diphtheria, 2 dysentery and 1 accompanied pulmonary tuberculosis. Nowadays, in large segments of the population, syphilis and diphtheria have practically vanished as etiologic factors. In the cases of chronic nephrosis in adults that I have seen, the etiology has almost always been obscure: edema appeared or proteinuria was discovered incidentally and careful questioning elicited no antecedent infection. In the much more frequent cases in young children, the onset sometimes follows an upper respiratory infection, such infections had occurred one to four weeks before the onset of edema in about 35 per cent of Heymann and Alperin's[37] patients But the nature of the connection, if any, between these infections and nephrosis remains to be elucidated I have been impressed by the contrast between the very high incidence of respiratory infection preceding acute glomerulonephritis and the much lesser frequency with which a history of such infection is elicited in nephrosis

Syphilitic Nephrosis.—The frequent occurrence of proteinuria in syphilitics was known even before the time of Bright, but was considered by Blackall[38] and other physicians of the time as always due to mercury used

The view that syphilitic nephrosis is due to mercury has been completely disproved by the observation of cases in which the patient had never been given mercury and improved directly after the administration of the drug. Moreover, even the
no edema, which is
litic nephrosis. Tha

sis* has been demonstrated especially by Munk,[1] though Dieulafoy[40] had previously observed the exclusively tubular localization of the lesions. Later, instances of syphilitic nephrosis were published by Herrmann and Marr,[41] Baker,[42] Patton and Corlette,[43] Moore[44] and others. In a patient at Mount Sinai Hospital who developed a classical nephrotic syndrome during secondary lues and succumbed to erysipelas due to the use of Southey tubes, necropsy revealed only anisotropic lipoidosis of the tubules.

Syphilitic nephrosis occurs almost exclusively during the secondary period of lues, the stage of the roseola and mucous patches. Dieulafoy gives the following dates of onset in 17 cases of syphilitic nephrosis: In 2 cases, eight months after infection, in 2, six months, in 2, four months; in 5, three months, in 5, two months Syphilitic nephrosis has been observed within a month of the primary lesion. *It is thus one of the* results of the generalization of the infection and is almost invariably accompanied by other manifestations, such as roseola, mucous patches, adenitis, etc. However, Vorpahl,[45] Schittenhelm,[46] and others have observed cases occurring years after the primary lesion In fact, Schittenhelm's patient suffered from two attacks of "typical luetic nephrosis," the first four years and the second six years after the infection, on each occasion improving

to be notable became the arsenicals and has ... ito use. However, the same is true of other secondary and tertiary manifestations of lues well known to Jonathan Hutchinson's generation Mild cases marked by only proteinuria are apparently more common; Peterson[47] found renal involvement in 3 8 per cent of cases of secondary syphilis According to

direct invasion of the kidneys by the spirochetes.

Other Infections —Chronic nephrosis may also follow infections other

* *Lipoid nephrosis is not the only* renal lesion that results from syphilis Rich[48] has described a *specific syphilitic nephritis* He observed this renal lesion in 13 of 200 necropsies on syphilitics Grossly, greyish-yellow flecks are seen in the cortex and the process may go on to scarring with irregularity of the surface The lesions consist in interstitial foci of lymphocytes, plasma cells and other mononuclear cells which may compress tubules Macrophages laden with cholesterol may be seen in the adjacent tubules and there may be interstitial lipid deposits The process seems to be a true

In extremely rare instances, diphtheria is complicated by chronic nephrosis.

Pneumococcus infections have also been considered as a cause of chronic nephrosis. Volhard noted that of 7 cases of chronic nephrosis, 4 died of pneumococcus peritonitis. Similar observations have been made by Holt and Howland, Bock and Mayer, Stolz,[51] McElroy, Schwarz and Kohn, and others. A number of such cases have occurred at Mount Sinai Hospital. Pneumococci have also been cultivated from other lesions (see p. 478) and from the blood by Schwarz and Kohn, McElroy and others. Blackman[11] has published a series of 10 cases of what he regards as pneumococcal lipoid nephrosis, and produced renal changes with edema in rabbits by the injection of pneumococcal toxin. Nevertheless, the question of the relationship of pneumococcus infections to chronic nephrosis is by no means settled. While some cases may be of pneumococcal origin, it seems likely that most pneumococcal infections in chronic nephrosis are secondary invasions, due to the greatly decreased resistance to infection which most patients with chronic nephrosis exhibit. For while infections with pneumococci are the most common in chronic nephrosis, other organisms may also be responsible; Schwarz and Kohn have repeatedly observed hemolytic streptococci to be the cause of bacteriemia and peritonitis in children with chronic nephrosis. In one of their patients, they were able to grow hemolytic streptococci and pneumococci from the blood on different occasions. Moreover, chronic nephrosis may be present for years before there is any evidence of infection with pneumococci or it may never be demonstrable. Finally, another fact which indicates that pneumococcus infections in chronic nephrosis are secondary is that they also occur in the nephrotic type of glomerulonephritis; I saw a number of cases of the nephrotic type of glomerulonephritis in which pneumococcus peritonitis developed. The origin of pneumococcus bacteriemia in patients with chronic nephrosis or the nephrotic type of glomerulonephritis is probably most often the upper respiratory and pulmonary infections from which they frequently suffer. The frequency of serious pneumococcus infections in chronic nephrosis has decreased greatly since the introduction of sulfonamides and especially antibiotics

Clausen and Marriott describe cases of chronic nephrosis in children which they believe to be due to infection with Staphylococcus aureus, particularly in the paranasal sinuses They have observed excellent results following appropriate treatment of the sinus infection Aldrich[52] also observed prompt improvement in children following the drainage of abscesses resulting from nasal infections Whether all of these cases were actually chronic nephrosis and not nephrotic forms of glomerulonephritis seems open to question. And it must be remembered that many cases of chronic nephrosis in children also recover under rational dietary treatment alone. Holt and Howland are not convinced of the especial etiological significance of staphylococcus infections of the sinuses. I have seen no evidence that infection of the paranasal sinuses is etiologically significant in chronic nephrosis or that treatment of such infection has any effect on the renal disease.

Cases presenting the clinical picture of chronic nephrosis are occasionally encountered in tuberculous patients, the *néphrite parenchymateuse des tuberculeux* of Landouzy and Bernard.[53] It seems probable, however, that ... f these cases are instances of amyloid nephrosis. At ... Bernard report

...

the nephrotic syndrome (edema, massive prot... and lipemia) which seemed to result from the therapeutic administration ... thadione (tridione) and cleared up on withdrawal of the drug. The ... observed to ... The produc- ...s) agent is of

...

Cryptogenic Chronic Nephrosis. ... cases, the etiology is veiled in dark... that they are of infectious origin ... these cases are primarily disorders of metabolism in which thyroid dysfunction plays an important role, and that the renal lesions are secondary to the constitutional disease His views are discussed further in the next section

Thrombosis of the Renal Veins.—Of great interest, despite its rarity, is ...

... by Shulman *et al*[54] The case I followed occurred in a patient originally observed by Dr Frederick Zeman, whom I also had the opportunity of studying On the patient's first admission to the hospital, he suffered from migrating phlebitis with thrombosis of the inferior vena cava Subsequently, he developed the classical nephrotic syndrome of two years' duration with anasarca, massive proteinuria, hypoproteinemia and lipemia, and succumbed to recurrent erysipelas Necropsy disclosed canalized thrombosis of the inferior vena cava and renal veins, as well as congestion and lipoidosis of the kidneys Evidently, in this case the obstruction to the venous return from the kidneys produced proteinuria sufficient to bring about the nephrotic syndrome I have seen another patient in whom the same diagnosis seemed plausible, but there has been no opportunity to verify it

THE NATURE OF CHRONIC NEPHROSIS

Because of the dominant role of protein... ... of the symp- ... lady logically ... ma and other

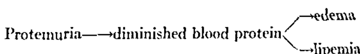
... of Proteinuria to the Symptoms of Chronic Nephrosis.—By far the most important, and often the only, symptom of chronic nephrosis is edema. The evidence is conclusive that the edema is a consequence of the proteinuria.

In the first place, the findings reviewed in Chapter 6 have definitely established Epstein's contention that the lower colloid osmotic pressure of the blood plasma due to the diminished albumin content is the essential cause of the edema, though other factors undoubtedly also influence the extent of the transudation.

Secondly, all evidence indicates that the loss of protein in the urine is the primary cause of the diminished protein content of the blood and the change in the relative proportions of the individual blood proteins. The protein lost in the urine is almost entirely albumin (over 90 per cent according to Hiller[59] and coworkers). This has been regarded as the explanation of why the albumin fraction of the blood protein is decreased so markedly; the conception is that regeneration is rarely able to keep pace with enormous loss through the kidneys. Little globulin and no fibrinogen are lost in the urine. However, Kerr, Hurwitz and Whipple[60] have shown
re rapidly than the other
Also, at least some cases
of chronic nephrosis are the result of infection, and the globulin and fibrinogen cont
facts, perhaps,
diminished and
gen is further discussed in connection with the blood chemistry.

Thirdly, it seems very probable that the lipemia and consequent lipoidosis of the kidney, which are so characteristic a feature of the disease that Munk termed it lipoid nephrosis, are likewise consequences of the proteinuria. The evidence for this view is discussed on p 473, where it is pointed out that it is still doubtful whether or not the proteinuria produces the lipemia through the intermediacy of hypoproteinemia

At the present state of our knowledge, therefore, the most probable interrelationship between the fundamental clinical manifestations of chronic nephrosis would seem to be represented by the following schema:



It does not seem too much to say that the relationship between proteinuria, hypoproteinemia and edema portrayed in this diagram are definitely established, questionable is only whether or not the proteinuria produces lipemia through the intermediacy of hypoproteinemia

The Question of Lessened Protein Synthesis in Chronic Nephrosis.—Strong evidence summarized above indicates that the primary basis of hypoproteinemia in chronic nephrosis is loss of plasma albumin in the urine. However, the suggestion has repeatedly been advanced that the protein waste in the urine may be abetted by quantitatively deficient regeneration of plasma albumin (*cf.* Bloomfield[61] and Weech *et al* [62]) This conception is based on the observation that hypoproteinemia may persist in nephrotic patients ingesting and assimilating amounts of protein greater than the sum of the protein breakdown in the body plus the protein lost in the urine. Actually, there seems to be no unequivocal evidence of a *primary* quantitative defect in protein synthesis in chronic nephrosis. While there

is no *exact* quantitative relation urine and the plasma albumin l very definite rough inverse correlation. ... if the proteinuria of a nephrotic patient falls to 5 grams or less daily and he assimilates an adequate protein diet of high caloric content, the plasma albumin level will rise. That this increase may be slow, and that weeks may pass before it is unequivocal, is hardly surprising. The plasma proteins are in equilibrium with perhaps several times as much ... hypoproteinemic patients both the intra-

[illegible]

slow and perhaps mask ... plasma protein ... are (1) expansion of p... proteinemia; and (2) t... the concentration of p... Various clinical obse... patient to synthesize ...

[illegible]

often seen asymptomatic individuals in whom massive proteinuria had been discovered during insurance or other examinations and had been present for at least months, and in whom the plasma proteins were within normal limits Such changes as have been observed in the relative proportions of the plasma proteins in chronic nephrosis (p. 471) are probably consequences rather than causes of the proteinuria; they are similar in all forms of the nephrotic syndrome, whether it results from chronic nephrosis, amyloidosis, glomerulosclerosis of glomerulonephritis Contrary to an earlier report by Farr and MacFadyen[66] that the plasma amino acid level is low in nephrosis, Gottfried *et al*[67] found these protein building blocks normal or even slightly elevated Lyttle *et al*[68] found that 8 of 9 children

[illegible]

exist in the nephrotic patient But it has not been demonstrated.

Cause of the Proteinuria of Chronic Nephrosis.—The next question that arises is that of the cause of the proteinuria. First to be decided is whether the proteinuria is due to an abnormality of the plasma proteins manifesting some extrarenal metabolic disorder, or whether the proteinuria is due to

renal disease entailing increased permeability of the kidneys to plasma proteins.

The Metabolic Theory of Nephrotic Proteinuria.—The theory that chronic nephrosis is primarily a metabolic [illegible] ... protein- [illegible] and the renal lesion only secondarily. But with the *débâcle* of humoral pathology at the hands of Virchow, *this conception was all but universally* abandoned until it was developed in its modern form by Epstein.[3] The present-day metabolic theory of chronic nephrosis is entirely due to the brilliant investigations of Epstein, who was the first of modern clinicians to appreciate adequately the extent to which copious proteinuria depletes the plasma protein and, in turn, the great significance of the latter for the pathogenesis of edema in "chronic parenchymatous nephritis." More recently, a metabolic theory of chronic nephrosis was advanced by the late Thomas Addis,[71] who regarded the disease as due to a defect in plasma protein formation, and coined the expression "prerenal proteinuria."

It is known that certain foreign proteins (*e. g.*, egg albumin, hemoglobin, Bence-Jones protein) free in the plasma are eliminated in the urine (but see p. 126). In accord with this fact Epstein believes that chronic [illegible]

[illegible] his belief in the metabolic origin of chronic nephrosis, Epstein has termed the disease "diabetes albuminuricus" He is of the opinion that impairment of thyroid function plays an important role in the genesis of chronic nephrosis. In support of this contention, he adduces the frequently lowered basal metabolism and beneficial effects he obtained in many cases of chronic nephrosis by the administration of thyroid extract Epstein has found that patients with chronic nephrosis have a remarkable tolerance for thyroid, whether given as the extract by mouth or as thyroxin intravenously, huge doses may be administered over long periods of time with few or no toxic symptoms and little elevation of basal metabolism. Epstein has observed a patient with chronic nephrosis who ultimately develops myxedema and two others in whom "chronic nephrosis supervened on prolonged irradiation of the neck, involving the chest and thyroid" In 8 cases of chronic nephrosis in children, Wolbach and Blackfan[11] have [illegible]

present in 10 necropsies on nephrotic children collated by Recant and Riggs.[72]

Investigations with modern methods do not indicate the presence of hypothyroidism in chronic nephrosis It is true that Peters and Mann[73] found that the protein-bound iodine in the serum is reduced in chronic nephrosis. This was also found by Recant and Riggs, who further noted that the basal metabolism is low even when calculated on the basis of edema-free weight. But they also demonstrated normal or supernormal uptake of radioactive iodine by the thyroid and a rise in the protein-

bound iodine level of the serum in response to thyrotropic hormone. Recant and Riggs interpret their findings as indicating normal thyroid function in chronic nephrosis—or even hyperactive to compensate for the ... and believe that the low protein-bound iodine

the kidney revealed no anatomical substratum ... Unfortunately, this case later showed the typical picture of chronic nephrosis. ... of the lack of details.

metabolism This theory lacks any substantial basis, we have seen ... probably is secondary to the changes in the blood proteins

prote...

1. ...

nephrosis are found ... diseases in which the renal origin of the proteinuria would seem beyond cavil

2 In the next section it will be seen that there is ample evidence that the kidney in chronic nephrosis is abnormally permeable to colloids. This points strongly to the renal origin of the proteinuria.

3 Hayman and Bender[75] found that injection of plasma from three patients with a nephrotic syndrome (one with chronic nephrosis) did not result in proteinuria in healthy recipients

4 The filtrability of molecules through the glomerular membrane is largely determined by their size (p 120) The possibility therefore immediately comes to mind that if the proteinuria of chronic nephrosis is due to abnormalities in the plasma proteins, the latter are of molecular size smaller than serum albumin, which has a molecular weight of 68,000 and

For these reasons, the metabolic theory of nephrotic proteinuria seems improbable

Increased Renal Permeability as the Mechanism of Proteinuria in Nephrosis —Proof of abnormal permeability of the kidney is afforded by the passage from the plasma into the urine of ... substance ... ounts of ... created ... t so ex-

this observation

. . . . . er[78] carried out quantitative ob- . . . ongo red, a colloidal dye, following intravenous injection. In health, the urine contained insignificant traces, but in patients with chronic nephrosis and other forms of the nephrotic syndrome, the dye appeared in the urine in concentration roughly proportional to the proteinuria.

(*c*) Bing[79] showed that if a patient with nephrotic proteinuria is given a blood transfusion, the quantity of albumin in the urine is increased while that of globulin is less affected. In view of the larger size of the globulin molecules, this is what would be anticipated from a rise in permeability of a certain degree. In the absence of renal disease, blood transfusion is not followed by proteinuria.

(*d*) When . . . en to patients with cirrhosis of tl . . . with renal disease, little or none . . . nephrotic patients are quickly followed by increase in albuminuria. Luetscher found that the increased protein excretion following injection of albumin is accompanied by little change in albumin clearance, which would indicate that it is eliminated by glomerular filtration.

(*e*) In the absence of kidney disease, for instance in the xanthomatous diseases, increase in the lipid content of the plasma does not result in lipiduria. But in chronic nephrosis considerable amounts of lipids pass from the plasma into the urine.

The increased permeability of the kidney indicated by the foregoing observations offers a satisfactory explanation of the fundamental phenomena of the nephrotic syndrome. It is readily conceivable that the increase in permeability is of such degree as to allow the smaller albumin molecules to pass through much more readily than the larger globulins, while the still larger fibrinogen molecules do not filter through at all. The lesion would thus produce effects analogous to the experiments of Krogh (p. 149), in which he increased the permeability of the capillaries so that they allowed the passage of starch, molecules but not of the larger India ink particles. The same order of increase in permeability to large molecules occurs in all forms of the nephrotic syndrome—chronic nephrosis, diabetic glomerulosclerosis, amyloidosis and glomerulonephritis. In each proportionately (to the plasma levels) more albumin than globulin enters the urine and fibrinogen does not pass through at all. In each, lipids and injected colloids enter the urine from the plasma. In each, the albuminuria produces hypalbuminemia and lowered colloid osmotic pressure of the plasma, and the latter results in edema. In each, lipid and protein (hyaline) droplets appear in the tubular epithelia, which is well explained by reabsorption from the filtrate which they have entered as a result of increased permeability. Increased permeability of the kidneys to large molecules explains the phenomena of chronic nephrosis so well—and likewise clears up so simply the occurrence of the same "nephrotic" syndrome in the four conditions of chronic nephrosis, renal amyloidosis, diabetic glomerulosclerosis and glomerulonephritis—that on mere clinical grounds it may be regarded as established. But in addition the urinary excretion of injected serum albumin and other large molecules furnish almost direct evidence of

the increased permeability of the kidney in chronic nephrosis. Practically the e... ...ture of chronic nephrosis seems to be a consequence of "leaky" kidn...

In ...

the ...

othe...

urine in more than minute amount ... arises of the mechanism by larger quantities The questio...

which, in nephrotic proteinuria ...

concentration into the urine ...

may be concerned:

1 An alteration in the walls of the glomerular loops such that more ...

albumin molecules (p. 125)

2 Decrease in the capacity of the tubular cells to reabsorb protein from ...

... available evidence points strongly to ... erular membrane as the fundamental mechanism of nephrotic proteinuria.

1 In fixed sections, coagulated protein is often found in Bowman's space

2 Of the commonly differentiated plasma proteins, albumin shows a far higher clearance than does the much larger globulin molecule, and the still larger fibrinogen does not enter the urine at all despite increase in concentration in the plasma Such behavior is in excellent accord with filtration through "pores" in the glomerular loops It will be interesting to learn how the molecular size of the individual globulins corresponds to their ...

... tion,

... ...llent.

Large amounts of ammonia are formed in response to the proper stimulus The urine is highly acid, which involves active tubular mechanisms Phenolsulphonephthalein is excreted in high concentration, which necessitates tubular excretion There is no defect in the tubular reabsorption of sodium, chloride or other electrolytes, while the question of glucose reabsorption is still unsettled (p 460). Tm for diodrast and p-aminohippurate are normal Since these variegated tubular functions are without exception unaffected, it seems improbable, though not impossible, that the tubular reabsorption of protein is impaired

4 Bing[88] found that during short periods exogenous creatinin clearance and proteinuria parallel one another Using the less inaccurate endogenous creatinin clearance as a measure of glomerular filtration, Eder et al [81] made similar observations They found that in the nephrotic patient the albumin clearance is independent of the plasma albumin level. Such behavior is much easier to reconcile with filtration as the primary mechanism of proteinuria than with an alteration in tubular transport

5. Eder and his associates calculated the minimum protein content of the glomerular filtrate—on the well-warranted assumption that protein is not excreted by the tubules—by dividing the albumin content of the urine by the volume of glomerular filtration (inulin clearance). They found that the glomerular filtrate of nephrotic patients contains between 115 and 305 mg./100 cc., which is far above what is believed to be the maximum protein content of the glomerular filtrate in health.

The proteinuria of chronic nephrosis would thus appear to be due fundamentally to increased permeability of the walls of the glomerular loops But it is possible that secondarily decreased reabsorption of protein from the filtrate by the tubular cells may augment the proteinuria. This could conceivably result from saturation of the protein-reabsorbing capacity of tubular epithelia which have taken up enough protein from the filtrate to exhibit "hyalin droplet degeneration," which is not a true degeneration but probably a morphological manifestation of the activity of the cell in taking up protein.

The Differentiation of Chronic Nephrosis From Glomerulonephritis.—Chronic nephrosis (lipoid nephrosis) was originally recognized as a nosologic entity by Munk, Volhard and Fahr, and Epstein. Very soon after, however, Loehlein[82] maintained that lipoid nephrosis is not a separate disease but a variety of glomerulonephritis. This opinion has since been supported by Elwyn,[83] Bell,[84] Moschcowitz,[85] and Allen,[86] and is widely accepted. The thesis that chronic nephrosis does not exist as an independent entity but is one of the forms of glomerulonephritis is largely based on the following supports:

1. The widely accepted rarity of cases with the clinical nephrotic syndrome which reveal purely degenerative renal lesions at necropsy (apart from amyloidosis and diabetic glomerulosclerosis)

2. The existence of cases which start as clinically typical acute hemorrhagic glomerulonephritis and then go on to develop the classical picture of the nephrotic syndrome without hematuria, hypertension or impairment of renal function Ultimately, these patients develop high blood pressure and generally succumb to renal insufficiency; necropsy may disclose what is regarded as chronic glomerulonephritis

3. The observation of patients who present the clinical picture regarded as typical of chronic nephrosis—massive proteinuria and edema of insidious onset without hypertension, hematuria or impairment of renal function—and nevertheless disclose chronic glomerulonephritis at necropsy.

The Anatomical Findings—A chief support of the theory that chronic nephrosis is a variant of glomerulonephritis has been the important investigations of Bell, to whom so much of our knowledge of the intimate histology of renal disease is due (p 448) On the basis of histological studies, Bell[10] championed the view that chronic nephrosis is actually a variety of glomerulonephritis. This investigator and his pupil McGregor performed the valuable service of introducing into the study of the pathological histology of the kidney modifications of Mallory's aniline blue connective-tissue stain, with this technique the glomerular basement membrane is brought out clearly so that the endothelial and epithelial cells of the glomeruli are more readily differentiated Using this stain,

Bell was able to demonstrate in cases of chronic nephrosis, in which the *glomeruli appeared* normal in the hematoxylin-eosin preparation, "an increase in the number and size of the glomerular endothelial cells and an uneven thickening of the basement membrane." As a result of these studies, Bell came to the conclusion that "lipoid nephrosis is to be regarded as a form of glomerulonephritis in which the glomeruli are damaged but their capi[illegible] obstructed so that they continue to function [illegible] findings, [illegible] with the staining methods which he recommends. [illegible] unable to demonstrate inflammatory glomerular lesions in either. It is true that they found swelling of the glomerular endothelial cells, which contained lipoid, but these cells were not increased in number. In the absence of proliferation—which, as they point out, is not mentioned in [illegible] Kantrowitz and Klemperer do [illegible]

Pick's disease, so that these lesions are [illegible] storage of lipoid derived from the lipemic blood Nor do they regard thickening of the capillary loops in itself as indicative of inflammation

Several subsequent investigations have shown that even with the most [illegible] in which [illegible]

of cases published in the valuable study of Murray [illegible] "no structural [illegible] appearance of the [illegible]" In his recent book on "Renal Diseases," Bell[84] comes to the conclusion that "From the histological point of view lipoid nephrosis is different from proliferative glomerulonephritis, but it is possible that the histological pictures merely represent different types of reaction to the same irritant" It would thus appear that the histological evidence does not support the concept that chronic nephrosis is a variety of glomerulonephritis

Regarding the interpretation of the histological findings, two further points seem worthy of consideration·

1 It is precisely in the classical [illegible] der [illegible] er- [illegible] in [illegible] microscopic [illegible] as glomerulonephritis, it would be precisely in [illegible] If chronic these cases of relatively short duration [illegible] young that inflammatory [illegible]

2 Wl[illegible] cumbed [illegible] widespread glomerular hyalinization [illegible] syndrome have succumbed [illegible] has been found at

nic glomerulonephritis has often been taken o doubt that in the past many cases of the in diabetics were thus misdiagnosed. Similarly, to the writer it seems that many such cases—in which there is no history of acute glomerulonephritis, in which proteinuria and edema set in insidiously, and in which glomerular hyalinization but no or trivial proliferative changes are found in the glomeruli—are instances of chronic nephrosis, the end stage of the process described in the section on pathological anatomy (p. 448). These constitute at least a very large proportion of the cases included by Ellis in his concept of Type II nephritis (p. 597).

It is widely believed that the diagnosis of chronic nephrosis is made too often and that many, if not all, the cases so diagnosed are actually instances of chronic glomerulonephritis. This belief finds its chief support in the dogma that all glomerular hyalinization apart from that due to arteriolosclerosis is indicative of chronic glomerulonephritis. However, a considerable number of instances of glomerular hyalinization formerly attributed to glomerulonephritis are now known to be due to the totally independent diabetic glomerulosclerosis. Similarly, other instances of glomerular hyalinization represent the end stage of chronic nephrosis In the opinion of the writer, most of the nondiabetic nephrotic syndromes in the elderly, which are almost always of insidious origin and without a history of acute glomerulonephritis, belong in this group of the hyalinizing end stage of chronic nephrosis

The Clinical Findings.—Some clinicians have been rendered sceptical of the existence of chronic nephrosis as an independent entity by following cases which for months or years present the classical picture of chronic nephrosis but then develop hypertension and renal insufficiency, succumb to uremia, and reveal at necropsy widespread glomerular hyalinization which is regarded as chronic glomerulonephritis But limitations in this chain of reasoning should be borne in mind·

(*a*) The clinical picture of the nephrotic syndrome results from depletion of plasma albumin (and the labile tissue protein or protein precursors with which it is in equilibrium) by albuminuria. Such depleting proteinuria may result from chronic glomerulonephritis, diabetic glomerulosclerosis, amyloidosis or chronic nephrosis In all these conditions the nephrotic syndrome *per se* is identical; differential diagnosis can only be made by accompanying identifying characteristics of the individual disease In the cases of chronic nephrosis these are all absent for long periods, *i. e.*, the patients suffers solely from the consequences of the proteinuria, which is why Epstein termed it diabetes albuminuricus In the large majority of instances of chronic glomerulonephritis, one or more such identifying characteristics as history of acute glomerulonephritis, hematuria, hypertension and impairment of renal function are present in the *early* stages But there are cases of chronic glomerulonephritis in which for a long period the symptomatology is almost purely that of the nephrotic syndrome resulting from massive proteinuria. In these cases it may be that the glomerular lesion causes relatively little obstruction to blood flow through the glomerular loops while damaging the walls so as to result in increased permeability. The fact that in such cases a differential diagnosis between

glomerulonephritis and nephrosis may be difficult to make for a long time does not gainsay the existence of chronic nephrosis any more than diag- ... in differentiating rheumatic from other forms of endo- ... endocarditis of ...

... develops hyper-

ment membrane in chronic nephrosis (p. 448) may ultimately so impede glomerular blood flow and obliterate so much of the filtering area that hypertension and renal insufficiency result. For beautiful examples of such a sequence of events, the reader is referred to the study of Fahr,[25] carried out in the clinic where the histology of the glomerulus has been ... carefully.

nephritis

The evidence at hand thu... of chronic nephrosis are not... They are noninflammatory... loops going on to hyalinization, and their etiology is in most instances obscure.

Summary.—The foregoing discussion of the pathogenesis of chronic nephrosis may be summarized briefly as follows:

The edema of chronic nephrosis is a consequence of the proteinuria.

The proteinuria is due to abnormally great permeability of the walls of the glomerular loops to large molecules, permitting the filtration of plasma proteins into the urine. If decreased tubular reabsorption of protein from the glomerular filtrate plays any part in the pathogenesis of the proteinuria, it is secondary.

The cause of the preternatural permeability of the walls of the glomerular loops ...

... membrane

In cases of true chronic nephrosis there is neither anatomical, nor symptomatic, nor anamnestic evidence that the damage to the glomerular loops is the outcome of antecedent glomerulonephritis ...

... hyaline droplet formation ... nation of the severity of the ... tubules. The lipidosis and

nephrosis

The functional characteristics of the renal alteration in chronic nephrosis are:

1. Increased permeability to colloids of the glomerular loops, evinced by proteinuria and lipiduria.

2. Unimpaired renal blood flow until late stages of the disease when hyaline thickening of the basement membranes obliterates glomerular loops.

3. Unimpaired tubular function, likewise until the late stages when the renal circulation is impeded.

Inasmuch as the lesion of glomerulonephritis can produce this combination for a long time, it is not surprising that this disease often simulates chronic nephrosis for years.

THE CLINICAL PICTURE OF CHRONIC NEPHROSIS

As a rule, the clinical picture of chronic nephrosis in the early stages is peculiarly monotonous; albuminuria and edema are the outstanding manifestations, waxing and waning with or without obvious reason over periods of months or years until the sufferer finally recovers, or goes on to renal insufficiency and uremia. The patient is weak and often pallid, though examination of the blood does not usually reveal as severe impoverishment in hemoglobin as the pallor would suggest. It is in chronic nephrosis that the "nephritic facies"—the combination of waxy pallor with edema—is seen in, perhaps, its most classical form

Onset.—The onset is usually insidious The patient feels weak and tires readily over a period of time which may be weeks or months, but usually does not go to the doctor until he notices an edematous swelling In young children the disease is most often discovered when the mother notes the dropsy, the child often feels well and is playful In adults the proteinuria is not rarely found in an insurance or other examination when there is no edema or subjective symptom. Rarely, in children, the disease has a sudden clinical onset with peritonitis or another infection. In the syphilitic cases, the first evidence of the disease may be the finding of protein in the urine in a routine examination during the course of antisyphilitic treatment. Or edema may be noted at the same time as the rash, sore throat or other manifestations of the secondary period of syphilis appear.

Edema.—Edema is the central feature of chronic nephrosis, to the patient it is the disease The hydropic swelling may start in the feet or in the face and usually spreads so as to become very extensive. It is peculiarly soft edema and the impression made by the finger is slow to disappear The scrotum or vulva may become enormously swollen Usually the serous sacs, notably the peritoneum, are also involved The edema may almost completely disappear from the skin while the ascites persists It is possible that some of the gastro-intestinal disturbances of which the patients often complain are due to edema of the mucous membrane, but I have not seen this proved. I have once seen edema of the retina.

The extent of the edema varies greatly Often, diminution is attributable to therapeutic measures, but in other instances there is no obvious explanation for the onset of diuresis and lessening of the edema. Then the

dema may increase again, though the regimen has been changed in no ay The edema may decrea following an acute infection (p. 492).

The edema fluid obtained f lear but may be opalescent leura, is almost always opal

able that this opalescence is due to the presence of a ... compound (Wallis and Schoelberg[88]) although Bruger[89] found no evidence of cholesterol-protein complexes in such fluids. The specific gravity of the fluid is very lov

The extremel Beckmann[90]). ... times I have found the protein content too low to be determined quantitatively Krogh[91] refers to a case of chronic nephrosis in which the edema fluid was protein-free As Schmidt[92] pointed out three-quarters of a century ago, the fluid of the ascites and hydrothorax contains much more protein than the anasarca fluid of the same patient Thus, Epstein found that the

content to average 3 3 per cent

the total protein content of the blood, because the factor of change in the proport 1 gram does 1 is apparently always present when the plasma protein content in nephrosis is less than 4 per cent (Linder[93] *et al*), and almost always when the plasma proteins fall below 5 per cent (Epstein) On the other hand, there may be nephrotic edema with almost 6 per cent of protein in the plasma if, as happens in unusual instances, this is mostly globulin The closest correlation is with the plasma albumin level, when the latter is below 2.5 per cent edema is rarely absent in a nephrotic patient In children, Gottfried *et al*[87] found that a rise in total protein above 4 0 or albumin above 1 5 per cent is almost invariably associated with decrease in edema, while a fall below these concentrations is almost always accompanied by increase in edema Of course, at any plasma albumin level the extent of the edema is influenced by other factors, notably sodium intake and therapeutic measures, which result in great changes in edema despite little alteration in plasma albumin concentration The question is discussed in more detail on p 157

Urine.—The urine is greatly diminished in volume while edema is forming or during periods when it is being held in check by fluid restriction. For

weeks at a time, the daily urinary output may be around 300 or 400 cc Corresponding to fluctuations in the edema, the urinary volume varies As the edema diminishes there may be marked polyuria. The urine is generally more or less cloudy and often of a smudgy brown color. On standing, it usually decomposes rapidly with the development of a nauseating odor.

During the oliguric periods the specific gravity of the urine is high, even after allowance is made for the protein present. Values over 1.030 are not very uncommon. The color is correspondingly deep, and a copious sediment of urates is often deposited. The urine is highly acid. As long as edema is forming the concentrations in the urine of sodium, chloride and bicarbonate are low, while those of urea, potassium, phosphate and hydrogen ions are high (*cf.* Fox and McCune[94]). With discharge of edema these changes are reversed. The alterations in the urinary solutes during accumulation of edema are compatible with simultaneous expansion of extracellular fluid volume, cellular dehydration, and augmented protein breakdown.

Proteinuria.—Proteinuria is a cardinal feature of chronic nephrosis. As a rule, the quantity of protein lost in the urine is very great. In fact, the highest degrees of proteinuria are observed in this disease, particularly in the syphilitic cases. One of Epstein's patients lost from 18.2 to 26.2 grams of protein in the urine daily for several months. In Descoust's[95] case of syphilitic nephrosis, there was the enormous amount of 110 grams of protein in 800 cc. of urine. Values of 2 per cent or more are not uncommon. The urinary protein is largely albumin. Hiller, McIntosh and Van Slyke[59] found that albumin constitutes over 90 per cent of the total urinary protein, a higher proportion than they found in other varieties of renal disease. The great predominance of the small albumin complexes in the urine in chronic nephrosis is also shown by measurements of the colloid osmotic pressure. Electrophoretic studies by Longsworth,[96] Luetscher,[97] Malmros and Blix,[98] and Routh[99] show the same peaks in the urine for albumin and alpha, beta and gamma globulins as does the plasma; fibrinogen, however, is absent despite elevated concentration in the plasma. The Tiselius pattern reveals an even higher proportion of the urinary protein to be albumin than does the Howe fractionation Only when the plasma albumin falls to extremely low levels is the preponderance of albumin in the urinary protein not so great Estimations of the molecular weight of the urinary albumin by Longsworth and MacInnes[100] indicate that it is less than of the albumin in the plasma, perhaps the smaller molecules are the more readily filtered During the administration of plasma or concentrated serum albumin, the urinary albumin content rises. Blackman and Davis[101] found the gamma globulin fraction very low in a patient with chronic nephritis, while it was much higher in rapidly progressive cases of the nephrotic form of glomerulonephritis; they suggest that the precipitation of gamma globulin, which is the fraction most readily thrown down by the usual protein precipitants, may be concerned in rapid progression of a nephrotic renal disorder

The proteinuria varies greatly from time to time. Diminution in proteinuria is usually accompanied by improvement of the patient, but it is prone to increase again The relation of the proteinuria to the diet is discussed on p. 122.

Slight and transient *glycosuria* is not uncommon. Hiller[102] showed that the urinary sugar in these cases is actually glucose. As Hetenyi[103] found, [illegible] at times confirmed, patients with chronic nephrosis almost [illegible] ingestion of 100 grams of [illegible]

[illegible] of patients with chronic nephrosis; in [illegible] glycosuria, the urine in the fasting state containing over 0.3 per cent of fermentable sugar and more than 1 per cent following the ingestion of 1 gram of glucose per kilogram body weight. The glycosuria is a "*renal*" glycosuria, for in several such instances in which the blood sugar was determined, the concentration in the blood did not reach the normal renal threshold for this substance. Possibly, the tubular lesions interfere with the resorption of sugar from the glomerular filtrate. It should be mentioned, however, that the renal nature of the alimentary glycosuria in chronic nephrosis is contested by Fell,[106] who found the renal threshold for glucose elevated and not lowered in this disease. His studies were carried out by the intravenous injection of glucose solution. It is not clear why t[illegible] should show a different renal threshold than that observed a[illegible]

[illegible] iment [illegible] ion of [illegible] ly the use of the polarizing device, which can be attached to any microscope. Viewed through the usual light, doubly refractile lipoids cannot be distinguished from fat and may pass for the ordinary granulations of a granu- la[illegible]

Notable quantities of doubly refractile lipoids occur in the urine not only in chronic nephrosis but also in other conditions in which there is lipoid degeneration of the renal epithelium, *i. e.*, diabetic glomerulosclerosis, the nephrotic type of glomerulonephritis and less commonly in amyloid nephrosis. Isolated anisotropic droplets found on one occasion are of little significance, occurring in many conditions; only the presence of considerable quantities in a single examination or of small amounts on repeated occasions is diagnostic of widespread lipoid deposition in the tubules.

The amount of anisotropic lipoids present in the urine in chronic nephrosis varies greatly; at times, there may be little or none while soon after

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amyloid nephrosis. The loss of blood proteins in these conditions, combined with the efforts of the body to regenerate the proteins and perhaps to compensate in other ways for their loss, produces characteristic changes in the proteins and lipids of the *plasma* The resulting "nephrotic blood picture," as it may be termed, consists essentially in the following:

1 Decrease in the total protein content of the plasma, usually entirely at the expense of the albumin fraction, with resultant inversion of the albumin to globulin ratio

2 Alterations in the proportions of the globulins.

3. Increase in the fibrinogen content of the plasma.

4. Decrease in the colloid osmotic pressure of the plasma.

... the velocity of sedimentation of the red blood cells.

these abnormalities of the blood resulting from copious ... discovery of which we are inclined to attribute wholly to modern chemical research Thus, Bostock[114] points out in Bright's first memoir that the blood is deficient in protein Bright's contemporaries were aware of the increase in fibrinogen in the blood of patients with marked proteinuria, in what seems to have been a case of chronic nephrosis, Schmidt[92] found 1 03 per cent of fibrin Christison[115] demonstrated the lipemia of such individuals

1 The decrease in the total protein content of the plasma is usually striking Instead of the normal 7 per cent or more of protein, there may be well under 3 per cent in severe cases It has already been mentioned that the drop in total protein is mostly or more often entirely due to diminution in the albumin fraction (see p. 456). The albumin concentration of the plasma may fall below 1 per cent in extreme instances. The result is that

globulin more than compensated for loss of protein in the urine, so that

than is indicated by the usual salting-out procedure. Luetscher[97] found electrophoretically that when albumin is decreased and alpha globulins

individual globulins (Longsworth,[96] Luetscher,[97] and Blix[117]) Usually, the

they are readily demonstrated. Gainsborough[107] found that while the urine normally contains from 1.7 to 4 mg. of cholesterol per day, the elimination in renal disease may be up to 41 mg. daily. Bruger[109] showed that the urinary lipids include cholesterol, fatty acids and phospholipids, and that all three lipids tend to vary *in parallel fashion*. *Lipiduria occurs only in the phases* of renal disease with pronounced proteinuria (apart, of course, from chyluria). Lipidemia in the presence of healthy kidneys does not produce lipiduria. Thus, in a diabetic with lipidemia so severe as to produce lipemia retinalis, I was unable to find lipids in the urine. *Lipiduria in the nephrotic syndrome has a twofold origin:* desquamation of tubular epithelium in which lipids have been deposited and filtration of plasma *lipids. The derivation* of some of the urinary lipids from desquamated cells is sometimes revealed by the finding in the sediment of renal epithelia containing lipid droplets. As a rule, however, the plasma is doubtless quantitatively a much more important source of the urinary lipids. This was indicated by the finding of Gross[108] that if a patient with chronic nephrosis or the nephrotic type of glomerulonephritis ingests 5 grams of cholesterol, the quantity of lipids in the urine increases greatly within a few hours. In diseases not characterized by massive proteinuria, Gross did

. [illegible] . iere is every reason to believe

. [illegible] . proteinuria, is a consequence of the increased permeability of the glomeruli. This conception of the filtration of lipids from the plasma into the urine is strongly supported by the finding of Bruger[109] and Bing and Starup[110] that the excretion of lipids parallels that of protein, as well as the observation of the latter investigators that the cholesterol excretion parallels the urea and creatinin clearances

The number of casts present differs, at times, there are numerous hyaline, granular and fatty casts, while on other occasions they are almost entirely absent. Leukocytes are usually present. Of great importance in the differential diagnosis from glomerulonephritis is the fact that red blood cells are completely absent or present in but very small numbers; well-marked hematuria does not occur in chronic nephrosis, apart from rare transitory episodes in which intercurrent infections may be concerned But that small numbers of erythrocytes do not rule out lipoid nephrosis is shown by Farr's[111] Addis counts, which disclosed an increased number of red cells in 19 of 36 children in whom he had made a diagnosis of nephrosis after six years observation. Carrying out Addis counts, Landis and Elsom[112] found that 3 patients with the nephrotic syndrome excreted between 200,000 and 800,000 red blood cells in twelve hours, which was much less than comparable patients with glomerulonephritis.

The Blood.—In chronic nephrosis there are abnormalities in the chemical composition of the blood which are of fundamental theoretical and practical importance These changes involve primarily the proteins and lipids of the plasma (*cf* Gutman[113] for a scholarly study of the plasma proteins in disease) The abnormalities in the plasma proteins and lipids evidently results from the loss of protein in the urine and are identical with those found in other diseases with copious and protracted proteinuriar, namely, diabetic glomerulosclerosis, the nephrotic type of glomerulonephritis and

...h will be discussed in the next paragr...

mg per cent) In fact, in a patient studied by Dr. George Baehr and seen by the writer, the cholesterol content of the blood attained the immense height of 2300 mg. per cent * According to the studies of Gainsborough[107] and Lichtenstein and Epstein,[12a] there is no characteristic change in the ratio of esterified to total cholesterol, which may fluctuate within wide limits In some of the patients studied by the latter investigators, as high

sis Knauer[35] found in the blood a total of 4700 mg per cent of fatty substances, of which 2500 mg per cent was fatty acids while cholesterol and phosphatides each constituted about 1000 mg per cent. In studies with accurate methods, Page, Kirk and Van Slyke[126] found that in the nephrotic syndrome free cholesterol, cholesterol esters, phosphatides and neutral fats rise and fall together Not only is the cholesterol content of the blood increased in chronic nephrosis, but it is also found in abnormally great quantities in the adrenals (Guy-Laroche[127]), and may be deposited in atheromatous patches in the arteries of young persons (Loewenthal[8]). We have already mentioned that lipoid may also be present in edema fluid in these cases

The pathogenesis of the lipidemia of the nephrotic syndrome requires further investigation Hiller[128] and her coworkers showed that the lipemia of chronic nephrosis is not the result of inability of the body to burn fat. The low basal metabolism found by Epstein and Lande[129] in some nephrotic

* Cholesterol is a comparatively insoluble substance, but nephrotic plasma carries
ate
be

alpha and
decreased,
extent, these changes in the globulins may be secondary to the albumin depletion, for Routh *et al.*[89] observed that they may be temporarily *reversed* by injection of concentrated serum albumin. The high beta globulin peak is partly correlated with the lipemia, for Longsworth and others have found that it is lowered after ether extraction. With the ultracentrifuge, Lewis and Page[226] found that in the nephrotic syndrome there is great increase in concentration of the S 70, 40–70, and beta and alpha$_2$ lipoproteins. The frequently very low gamma globulin content may play a part in the susceptibility of nephrotic patients to infections, for many antibodies are included in the gamma globulin fraction.

3. Kollert and Starlinger[118] pointed out, and others have confirmed, that in chronic nephrosis there is an increased fibrinogen content of the plasma. Normally, the plasma contains less than 0.3 per cent of fibrinogen, while in chronic nephrosis Kollert and Starlinger found as much as 1.19 per cent. The cause of the rise in fibrinogen is not definitely known. Fibrinogen is increased in the blood in many infections, but it scarcely seems that this factor can account for the great increase seen in chronic nephrosis. Kollert and Starlinger believe the increase in fibrinogen to result from increased destruction of tissue protein which, according to these authors, occurs in chronic nephrosis. The explanation seems hypothetical (see also p 456)

4. That the colloid osmotic pressure of the blood plasma is markedly decreased in chronic nephrosis was pointed out by Epstein on the basis of his observations of the decreased protein content of the plasma. This decrease in colloid osmotic pressure and its relation to the edema have been repeatedly established by direct measurements, which have revealed that the fall in colloid osmotic pressure is proportionately greater than the drop in protein content. These researches are summarized on p. 157.

5. Kollert,[119] Salomon[120] and others have shown that the sedimentation time of the red blood cells is markedly diminished in the nephrotic syndrome. Some of the fastest sedimentation rates are seen in this condition, a Westergren sedimentation rate of over 120 mm per hour is not rare. This is evidently a result of the changes in the colloids of the plasma; in fact, Salomon has shown that a relative rise in the globulin fraction is practically always accompanied by decreased sedimentation time The high fibrinogen and low albumin contents of the plasma may also be concerned, for these changes in the plasma proteins have been observed to be related to acceleration in the sedimentation rate. Block *et al*[29] found that in nephrotic children acceleration of the sedimentation rate is more closely correlated with fall in albumin than with rise in fibrinogen.

6. The milky appearance of the blood serum in some nephropathies with copious proteinuria was observed first by Blackall[39] and Bostock.[114] Christison[115] showed that it is due to the presence of fat in the serum. This may be but slightly cloudy or almost milky. That this lactescence of the serum is due not only to fat but also to lipoid was shown by Port and Chauffard, *et al.*[121,122] who found that there may be marked hypercholesteremia. The lactescent appearance of the serum is probably due to the formation of a lipoid-globulin compound. Lipemia and lipoidemia are almost constant

features of chronic nephrosis and the nephrotic type of glomerulonephritis. An exception is found in emaciated patients, in whom they may be absent for reasons which will be discussed in the next paragraph. In amyloid ... there is usually severe emaciation, the cholesterol ... the patient is well ... yloidosis or glomer- ... usually accompanied

in rare instances may even exceed ... mg. per cent). In fact, in a patient studied by Dr. George Baehr and seen by the writer, the cholesterol content of the blood attained the immense height of 2300 mg per cent.* According to the studies of Gainsborough[126] ... there is no characteristic change in the

syndrome free cholesterol, cholesterol ... fats rise and fall together Not only is the cholesterol content of the blood increased in chronic nephrosis, but it is also found in abnormally great quantities in the adrenals (Guy-Laroche[127]), and may be deposited in atheromatous patches in the arteries of young persons (Loewenthal[5]). We have already mentioned that lipoid may also be present in edema fluid in these cases

The pathogenesis of the lipidemia of the nephrotic syndrome requires further investigation Hiller[128] and her coworkers showed that the ...

... not closely correlated with hyperlipemia. Heymann and Clarke[129] observed lipemia following nephrectomy or renal damage by poisons, but it is difficult to see the connection of this with the nephrotic syndrome, in which lipemia is present while renal function is unaffected and tends to disappear if azotemia develops. E. H Fishberg[131] and the writer found that in experimental lipemia produced by bleeding rabbits, the rise

* Cholesterol is a comparatively insoluble substance, but nephrotic plasma carries

alpha and beta globulins are markedly increased and the gamma globulins decreased, while variable changes are reported in $alpha_1$ globulins. To some extent, these changes in the globulins may be secondary to the albumin depletion, for Routh *et al.*[99] observed that they may be temporarily reversed by injection of concentrated serum albumin. The high beta globulin peak is partly correlated with the lipemia, for Longsworth and others have found that it is lowered after ether extraction. With the ultracentrifuge, Lewis and Page[226] found that in the nephrotic syndrome there is great increase in concentration of the S 70, 40-70, and beta and $alpha_2$ lipoproteins. The frequently very low gamma globulin content may play a part in the susceptibility of nephrotic patients to infections, for many *antibodies are included in the gamma globulin fraction.*

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they · and Benedict[134]
long ago ... is diminution in
total base is due to recession in sodium... Cune[89] found the average serum sodium of their nephrotic children 132 mEq. per liter as contrasted with their normal average of 142 mEq. There is little change in the *potassium* content of the serum (Kohn[197]). Salvesen and Linder[234] showed that the serum *calcium* content is depressed; less than 6 mg. per cent is not rare and values as low as 3.5 mg. per cent occur. Salvesen and Linder correlated the hypocalcemia with hypalbuminemia; the fraction of the calcium which is bound to protein is lowered. This interpretation ... the finding of Gottfried et al.[57] that the serum calcium,

not decreased
tetany, and ...
frog's heart ...
the anions, Atchley and Benedict observed long ago that ... may be elevated and *bicarbonate* depressed, and similar findings have recently been obtained by Fox and McCune Atchley and Benedict observed that ... tration of chloride leads to very pronounced rise in the plasma

normal limits
In recent years, since the flame photometer has made sodium and potas- ... more or less routine, the writer has most often seen

in children Usually only when hypoproteinemia is complicated ...
insuffic... to glomerular hyalinization or some such transitory
pretena...
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persist While the lowered albumin content of the plasma affects the electrolyte concentrations through the mechanism expressed in Donnan's formulation, the changes due to this factor alone apparently are not marked.

Gottfried *et al*[57] found the serum *carotene* level elevated in most nephrotic children, this may be correlated with the lipemia

As regards the *blood volume*, older observations of Brown and Rowntree[141] with the dye method indicated that in the absence of anemia the blood and plasma volumes are normal, but when there is anemia both these volumes are increased However, in the nephrotic syndrome the dye method is probably even less reliable than under other circumstances because of the rapid departure of colloidal dyes from the circulation (*cf* next paragraph) Using the carbon dioxide method, Waterfield[217] found the blood and plasma volumes lowered in the nephrotic stage of chronic glomerulonephritis, in which the conditions are presumably anal-

in fat and lipoid is correlated with fall in plasma protein. In these experiments it was found that the fat and lipoid accumulating in the blood were derived not only from the food but also by mobilization from the subcutaneous tissue and other fatty depots, which were completely stripped of their normal fat. In chronic nephrosis in humans there is also loss of the subcutaneous fat, though it is masked by the edema, and it seems probable that the mechanism of nephrotic lipemia also consists in mobilization of lipids into the blood from the food and the lipid depots consequent on the fall in blood protein. It may be that the lowered protein content of the plasma creates physical conditions which favor the migration of lipids into the plasma. A teleological explanation of the lipid mobilization, as yet unproved, is that it is an effort on the part of the body to increase the abnormally low colloid osmotic pressure of the plasma that results from the loss of protein in the urine. According to this theory, the reason for the frequent absence of lipemia in emaciated patients with low blood protein—notably those with amyloid nephrosis—is the paucity of fat in the depots and the poor appetite of most such individuals, so that little lipid is available for mobilization into the blood stream. Evidence indicating that the lipids of the plasma actually exert a colloid osmotic pressure has been advanced by E. H. Fishberg,[132] although Peters[133] believes that this pressure is small. Keys and Butt[134] find that the capillaries of man are as impermeable to the serum lipids as they are to proteins, but nevertheless were unable to demonstrate that the lipids exert a colloid osmotic pressure.

However, this conception, that the lipemia of the nephrotic syndrome is a consequence of the hypoproteinemia, has not been generally accepted. Strongly opposed to it is the finding of Leiter that when the plasma proteins of the dog are depleted by plasmapheresis, the blood cholesterol does not rise. Moreover, Page, Kirk and Van Slyke,[126] Bing and Starup[110], and Peters and Mann[73] found no close correlation between plasma protein deficit and lipemia in the nephrotic syndrome. Hypoproteinemia due to undernutrition in man is rarely accompanied by lipemia. While these facts speak against the theory that nephrotic lipemia is a consequence of hypoproteinemia, they do not rule it out because the development of lipemia may be prevented by undernutrition and consequent exhaustion of the fat depots. Clinical observations indicate that the lipemia is in some way a consequence of the proteinuria I have repeatedly observed that diminution in proteinuria for more than a transitory period is accompanied by decrease in lipemia. When a patient with the nephrotic form of glomerulonephritis develops renal insufficiency, the resulting decrease in proteinuria is associated with diminution in lipemia.

The *crystalloids* of the blood are usually less affected unless the patient goes on to the stage of glomerular hyalinization with renal insufficiency. Until this late stage, the *urea* and *nonprotein nitrogen* levels are within normal limits. During pneumococcus peritonitis or other complicating infections, or as a result of vomiting or diarrhea from any cause, transitory azotemia may develop The administration of urea as a diuretic in combination with high protein diet often raises the blood urea.

The *electrolyte* constellation varies considerably from case to case Often the electrolytes are within normal limits, while in other patients

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corre... filtration (inulin clearance), they conclude ... augmented renal blood flow.

... son's observation that it may persist long after ... to normal And O'Leary and Corson[148] have found that renal blood flow and glomerular filtration change little when the plasma proteins of dogs are diminished by plasmapheresis.

Such tubular fu... have been studied in lipoid nephrosis are likewise intact (ex...

... the urine ammonia is not impaired ...

... impairment of renal function and uremia develop ...

Basal Metabolism.—Ox... nephrosis (Epstein), even ... and Van Slyke[48]) Most ... −20 per cent being found, ... present In other cases the basal metabolism is normal Epstein's views on the nature of the metabolic disturbance in chronic nephrosis are discussed on p 458 Another factor that may also be concerned in depressing the basal metabolism in chronic nephrosis is undernutrition Most patients with chronic nephrosis suffer from undernutrition and protein starvation (Peters[149]) One of the mechanisms by which the organism adapts itself to undernutrition is by depressing oxygen consumption.
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C... the edema being the only complaint. One is often surprised how edematous children play without discomfort. But after a variable time weakness appears and may become extreme The emaciation is actually very great, but is usually hidden by the edema The appetite is, as a rule, very poor which renders the all-important abundant feeding of the patient very difficult This difficulty is sometimes enhanced by vomiting and diarrhea, perhaps due to edema of the gastro-intestinal mucous membrane After a time, most adults become discouraged and despondent because of the apparently interminable dropsy, for which the physicians seem able to do so little

ogous to those in chronic nephrosis. Observations of low plasma volume in the nephrotic syndrome have also been made by Luetscher[218] and by McClure[219] *et al.*; this seems to be at least the rule while edema is forming or being maintained.

Colloidal dyestuffs injected into the blood stream of patients with chronic nephrosis disappear f
The rapid disappearance of C
as a test for amyloid disease by Bennhold (see Chapter 18), but it also occurs in chronic nephrosis and the nephrotic type of glomerulonephritis. Thus, one hour after the intravenous injection of Congo red into a patient with chronic nephrosis, only 18 per cent of the dye remained in the blood stream, instead of a normal of 70 per cent or more. The cause of the rapid disappearance is discussed in Chapter 18 and p. 460.

Clausen[142] and Leiter[143] have found that the *surface tension* of the blood serum is lowered in chronic nephrosis, a phenomenon which probably results from the diminished protein content.

Anemia.—Despite the striking pallor of most patients with chronic nephrosis, anemia, in contrast to glomerulonephritis, is present in only part of the cases and is most often not marked. Brown and Rowntree[144] found the hemoglobin content of the blood normal in 5 of 9 cases of chronic nephrosis, while the anemia was but mild in the others In a subsequent study, using more rigid criteria for the diagnosis of chronic nephrosis, Wilbur and Brown[144] observed anemia in but 1 of 25 cases, a proportion which is well below my experience. In some cases, particularly if there has been long-continued dietary restriction, the anemia may be very severe Contrary to azotemic anemia, it is a hypochromic anemia with a low color index.

Blood Pressure.—The blood pressure is normal in chronic nephrosis in children and usually for years in adults. But in those cases which go on to extensive glomerular hyalinization with obliteration of capillary loops, the blood pressure rises and pronounced hypertension may develop Contrary to the generally held opinion, accepted in the previous editions of this book, such evolution of hypertension does not necessarily signify that a nephrotic syndrome is due to glomerulonephritis (p. 465). With hypertension, the previously unchanged heart hypertrophies.

Renal Function.—Corresponding to what the histological findings would lead one to anticipate, renal function is excellent in chronic nephrosis in children of extensive glomerular hyaliniz , even after allowing for protein, ty is high, and the urea content may exceed 3 per cent. Azotemia is absent; in fact, blood urea nitrogen of less than 10 mg per cent is common in nephrotic children. Phenolsulphonphthalein is promptly excreted The concentration test shows ability to form urine of specific gravity over 1.030

Glomerular filtration is not only unimpaired but the important studies of Emerson and his coworkers[145] have shown that it is often supernormal In 14 of their 33 nephrotic children under the age of ten years, the urea clearance exceeded 140 per cent of the average normal; one of them had a urea clearance of between 200 and 300 per cent for six years. Supernormal

urea clearances were not observed in patients over eighteen years of age. Since Emerson *et al.* found that the high urea clearance accompanied correspondingly increased renal blood flow (diodrast clearance) and glomerular filtration (inulin clearance), they concluded that the increased urea clearance in nephrotic children is due to augmented renal blood flow. That the increased filtration is not purely a consequence of decreased

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As mentioned above, transitory impairment ... azotemia may result from vomiting, diarrhea or infection. Only in those cases which go on to extensive hyalinization of the glomeruli do permanent impairment of renal function and uremia develop

Basal Metabolism.—Oxygen consumption is often lowered in chronic nephrosis (Epstein), even after allowance is made for the edema (Peters and Van Slyke[148]) Most often, the lowering is but slight, values such as −20 per cent being found, though even lower oxygen consumption may be present In other cases the basal metabolism is normal Epstein's views on the nature of the metabolic disturbance in chronic nephrosis are discussed on p 458 Another factor that may also be concerned in depressing the basal metabolism in chronic nephrosis is undernutrition Most patients with chronic nephrosis suffer from undernutrition and protein starvation (Peters[149]) One of the mechanisms by which the organism adapts itself to undernutrition is by depressing oxygen consumption.

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The *liver* is often palpably enlarged in nephrotic children. Fatty, vacuolar and other regressive changes may be found histologically (Block *et al.*,[29] Blackman[17]); most often, these alterations are slight. Gottfried and his associates[67] found that the thymol turbidity and cephalin flocculation tests often give abnormal results in nephrotic children but sulfobromphthalein excretion are normal and alkaline phosphatase values are not elevated. In adults, Boyd[151] found no evidence of damage to hepatic function in the nephrotic syndrome with the cephalin flocculation and thymol turbidity tests, the serum bilirubin, and the urinary urobilinogen The liver damage is not severe and hardly clinically significant; it may well be secondary to the hypalbuminemia, for Elman and Heifetz[152] found that the hypalbuminemia of dogs on protein deficient diets is associated with vacuolization of the liver cells There is no evidence that damage to the liver is responsible for the hypalbuminemia of nephrosis; the high content of the plasma in fibrinogen, which is also formed by the liver, bespeaks no diminution in the ability of the liver to synthesize protein.

Generalized *skeletal decalcification* was observed uniformly in nephrotic children by Emerson and Beckman.[153] Their *x*-ray studies revealed that the rarefaction is [illegible] while the epiphyseal lines exhibit [illegible] ormally and have no evidences of [illegible] Emerson and Beckman attribute the rarefaction of the shafts of the bones to the abnormally great loss of calcium in the feces which they demonstrated Calcium is almost absent from the urine; this is presumably a result of the low calcium content of the blood

On rare occasions, even in children, symptoms due to arterial or venous *thrombosis* occur. In Schwarz and Kohn's[33] patient, thrombosis of a cerebral artery caused sudden death

Secondary Infections.—Patients with chronic nephrosis are very susceptible to infections. This may be correlated with diminution in antibodies included in the gamma globulin fraction of the plasma (p 472). By taking repeated blood cultures, Schwarz and Kohn[33] were able to demonstrate bacteriemia at one time or another in 6 of 9 children with chronic nephrosis In most instances the organism was pneumococcus Type IV, but hemolytic streptococci were also grown on several occasions and pneumococcus Type III in one patient Invasion of the blood stream occurred in one of their patients on four different occasions, three times with pneumococcus Type IV and once with hemolytic streptococcus. We have already mentioned that the most frequent portal of entry of the infection is probably the respiratory tract. Especially in children, the clinical manifestations associated with bacteriemia in chronic nephrosis [illegible] days. Schwarz [illegible] In the one, the symptoms were peritoneal with abdominal pain, vomiting, distention, rigidity and tenderness also present on rebound; all of these symptoms cleared up within a few days Some of their patients had a number of such attacks. In the other children with positive blood cultures the manifestations were those of an upper respiratory infection, with exudate often present on the uvula or rhino-pharynx.

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In many cases, these metastatic infections are not so mild and there may develop fatal peritonitis or bronchopneumonia Before the introduction of sulfonamides and penicillin, pneumococcus peritonitis was probably the most common cause of death in chronic nephrosis. The peritonitis seems to be due to infection of preexistent ascites Usually, the peritonitis is diffuse but it may be localized, pneumococci are generally found in spreads but may be difficult or impossible to grow. The onset may be as in the mild episodes just described, but the fever then rises and the rigidity, vomiting and peritoneal facies become more marked In other cases the clinical picture is severe from the very onset, one such patient was considered to have a perforation of the appendix and was operated upon under this diagnosis Abdominal puncture and examination of the spread for pneumococci may establish the diagnosis in doubtful instances In pre-sulfonamide days
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this twice in adults, and Schwarz and Kohn, Fanconi,[147] and others reported recoveries in children, in whom such a favorable termination was *more* common than in adults Since sulfonamides and especially penicillin have been available, the course of pneumococcus peritonitis has been completely changed, almost all the cases quickly respond

Other infections may also occur Schwarz and Kohn observed in a number of their children an erysipeloid lesion of the skin which lasted a few days, in one case an abscess formed, from the pus of which they cultured a pneumococcus The lesion occurs *most often on the* abdomen and thighs, but may appear elsewhere, it may be very transitory or last over a week and is generally accompanied by fever. Erysipeloid is apt to recur I have seen fatal erysipelas following subcutaneous drainage. Stolz[37] cultivated pneumococci from a pleural effusion and Munk[94] the same organism from an abscess in the myocardium Bronchopneumonia was formerly a common cause of death But nowadays these infections, like pneumococcus peritonitis, generally respond promptly to penicillin

Recurrent Chronic Nephrosis.—Derow[159] has described a case in which the nephrotic syndrome recurred three times in fifteen years. Between the episodes, the patient was without albuminuria, edema, hyalbuminemia or hypercholesteremia; all of these were present during the recurrences. What seem to be similar cases were described by Addis.[160] Recently, I saw a child of four years with lipoid nephrosis in whom a ten day course of ACTH was followed by complete remission; after seven months of negative urine, for no apparent reason, the proteinuria and then the edema recurred.

THE DIAGNOSIS OF CHRONIC NEPHROSIS

The chief diagnostic problem which arises is the differentiation of chronic nephrosis from the other diseases in which the clinical picture is characterized by copious proteinuria and severe edema, namely, the nephrotic type of glomerulonephritis, diabetic glomerulosclerosis, and amyloidosis.

The decision whether a patient suffers from the nephrotic type of glomerulonephritis or chronic nephrosis is often very difficult Of course, the definite history of onset with acute glomerulonephritis (hematuria, hypertension, following scarlet fever, etc.) decides for chronic glomerulonephritis, but this is absent in many instances of the disease. Cases of glomerulonephritis may present for many months or years a clinical picture which simulates in every detail that of chronic nephrosis There may be insidious onset, great edema, normal blood pressure, intact renal function, normal retina, marked proteinuria, doubly refractile lipoids in the urine, absence of hematuria, and the nephrotic blood picture. It is such cases, in which the clinical diagnosis of chronic nephrosis has been made and which are found at necropsy to have chronic glomerulonephritis, that have caused some to be skeptical of the existence of chronic nephrosis. Prior to the age of five years, chronic nephrosis is much more common than chronic glomerulonephritis. In later childhood and adult life up to the age of about sixty the reverse is true. In the aged, the proportion of nephrotic syndromes due to chronic nephrosis is higher. The presence of even a few red cells in the urine or the development of renal insufficiency or hypertension have often been regarded as conclusive evidence that a patient has glomerulonephritis However, a small number of erythrocytes (less than 10 per high power field) in some of many examinations is common in nephrosis, and on rare examinations the urine of children ultimately proved anatomically to have chronic nephrosis exhibits many more erythrocytes. And in long standing lipoid nephrosis, hypertension and renal insufficiency may result from hyaline obliteration of many glomerular loops In my experience, however, this has occurred only after years of a nephrotic syndrome uncomplicated by hypertension or impaired renal function; cases in which the nephrotic syndrome evolves *pari passu* with hypertension and/or renal insufficiency have glomerulonephritis. There are many instances of the clinical nephrotic syndrome in which *intra vitam* differentiation between chronic nephrosis and glomerulonephritis is not possible The writer would like to repeat that in his opinion the pendulum has swung too far toward
the nephrotic syndromes of the elde
glomerular hyalinization with no evid

The diff
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disease, such as ...
settles the diagnosis. Or there may be other evidences of amyl...
such as enlargement of the liver and spleen or persistent diarrhea. But
even if such evidence of amyloidosis of other organs cannot be detected
clinically, a nephrotic picture in the presence of a cause for amyloid disease
... loid nephrosis The Congo red test (p. 525)

Chronic nephrosis occurring in the secondary stage ...
presents no diagnostic difficulties If mercury has been given, the question
arises whether t ... is not due to the drug. If there is marked
edema, it may l
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Occasionally, especially in infants and young children, there may be
some difficulty in differentiating chronic nephrosis from edema due to
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both conditions, but in nutritional edema there is generally a normal or
low cholesterol content of the blood In this connection, however, it
should be remembered that in cachectic patients with chronic nephrosis
lipemia may also be absent, though this is very rare.

THE PROGNOSIS OF CHRONIC NEPHROSIS

Some of the cases in which a diagnosis of chronic nephrosis is made after
The prognosis has improved
od penicillin, and perhaps even
, but even in pre-antibiotic days
there were many recoveries This was particularly the case in children, in
whom Holt and Howland lost *only* 2 of 20 cases, both of pneumococcus
peritonitis and pneumonia. On the other hand, Schwarz and Kohn lost 5
of 9 children with chronic nephrosis Later they reported that of 40 children with lipid nephrosis studied during a period of twenty years, 22
succumbed Of 40 *nephrotic children observed* by Block *et al.*[23] during a
fifteen year period, 26 are alive, 19 have been entirely well for one to
sixteen years, 3 have been well for less than a year, and 4 still have the

reported 4 cases of chronic nephrosis in adults which recovered completely after illnesses lasting from one to ten years; in 4 of his other patients there remained only asymptomatic proteinuria. I have seen only a few recoveries drom chronic nephrosis in adults. In 2 patients who got well proteinuria had been present for about ten years. In the recoveries that I have seen in adults the proteinuria was almost always discovered incidentally and the patient had little or no edema, although changes in the plasma proteins and lipids characteristic of the nephrotic syndrome were present. Of course, in the patients who recover the question of the certainty of the differentiation from chronic glomerulonephritis arises. I have not seen recovery in chronic nephrosis setting in after the age of forty. In most instances the disease is very protracted, dragging out over months and years, with periods of remission and exacerbation. Perhaps no disease is more trying to the patience of patient and doctor alike. Even when slight proteinuria is the only remaining evidence of the disease, there is always danger of a relapse. In some cases the edema clears up, but the patient remains with proteinuria for years (thirty-two years in one case) while he is able to continue at his work. Or the patient may have periods of slight edema which do not inconvenience him notably.

In former years the chief cause of death in chronic nephrosis was infection, notably pneumococcic and other varieties of peritonitis, bronchopneumonia, and pneumococcic or streptococcic bacteremias, erysipelas was a danger notably after subcutaneous drainage The incidence and mortality of these infections has diminished greatly since the introduction of sulfonamides and antibiotics.

Paradoxically enough, intercurrent infections, notably with measles, may be followed by improvement (p. 492)

In adults, after a varying number of years which may extend to decades, hypertension and impairment of renal function may develop and the patient succumb to uremia or some cardiac or cerebral manifestation of hypertension and arteriosclerosis. As indicated above (p.465), this course results from glomerular hyalinization.

The cases occurring in the secondary stage of syphilis usually respond
take a long time before the
There are cases of chronic
which antiluetic treatment is of no avail. In one such case reported by Dieulafoy, the edema persisted and death from erysipelas occurred on the forty-fifth day. I have also seen a case of this kind in which antiluetic treatment did not help and when subcutaneous drainage was attempted, fatal erysipelas ensued

THE TREATMENT OF CHRONIC NEPHROSIS

Apart from the now almost extinct syphilitic cases, there is no specific etiologic treatment for chronic nephrosis. The main measures in use are:

1. Sodium restriction
2. Correction of protein starvation.
3. Intravenous infusion of plasma or serum albumin.

4. Administration of ACTH or cortisone.
5. Prevention and treatment of intercurrent infections

Sodium Restriction.—As in all edematous states, sodium restriction is fundamental in the treatment of chronic nephrosis. Often, although not always, reduction in sodium intake is followed by diminution in edema, and aggravation results from increase in the sodium ration. A low sodium diet is indicated in almost all nephrotic patients with edema. During edema-free periods more salt may be allowed if the patient craves it. But he should

Care s

hot weather or considerable physical exertion.

are discussed in the section on treatment of edema (p 174).

While sodium restriction constitutes one of the cornerstones in the management of nephrotic edema, Osman[187] long ago pointed out that diuresis sometimes follows

acetates in nephrosis is due to rectification of abnormalities in the electrolyte economy—including lowering of sodium and bicarbonate in the plasma and retention of chloride and depletion of potassium in the cells—resulting from deficient renal regulation, and that with this correction lowered plasma volume, glomerular filtration, and renal excretion of sodium and water are augmented. The mechanism of the diuresis that occasionally follows the administration of large quantities of sodium and potassium acetates is not clear to the writer. Some special constellation of the electrolytes must be present, for more often in nephrotic patients diuresis is not produced by large doses of sodium and potassium salts and frequently the edema increases.

The *water intake* should be regulated by the thirst of the patient unless there is dehydration or vomiting necessitates parenteral fluids (p. 172).

Correction of Protein Starvation.—The treatment of chronic nephrosis, apart from the syphilitic cases, revolves primarily about the regulation of the diet. Formerly, the dietetics of chronic nephrosis was much the same as that of other varieties of Bright's disease, rigorous restriction of protein being generally practised.* But the brilliant investigations of Epstein changed then prevelant views of the proper regimen in chronic nephrosis, and it has been widely realized that not only is protein restriction not beneficial in this disease but that, on the contrary, it is very often detrimental for the following reasons

1 Patients with copious and protracted proteinuria need sufficient protein to replace not only the tissue protein broken down in metabolism

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... gave 100 to 150 grams daily of white of egg. He failed completely and even his attempt was forgotten

reported 4 cases of chronic nephrosis in

I have seen only a few recoveries from chronic nephrosis in adults. In 2 patients who got well proteinuria had been present for about ten years. In the recoveries that I have seen in adults the proteinuria was almost always discovered incidentally and the patient had little or no edema, although changes in the plasma proteins and lipids characteristic of the nephrotic syndrome were present. Of course, in the patients who recover the question of the certainty of the differentiation from chronic glomerulonephritis arises. I have not seen recovery in chronic nephrosis setting in after the age of forty. In most instances the disease is very protracted, dragging out over months and years, with periods of remission and exacerbation. Perhaps no disease is more trying to the patience of patient and doctor alike. Even when slight proteinuria is the only remaining evidence of the disease, there is always danger of a relapse. In some cases the edema clears up, but the patient remains with proteinuria for years (thirty-two years in one case) while he is able to continue at his work. Or the patient may have periods of slight edema which do not inconvenience him notably.

In former years the chief cause of death in chronic nephrosis was infection, notably pneumococcic and other varieties of peritonitis, bronchopneumonia, and pneumococcic or streptococcic bacteremias; erysipelas was a danger notably after subcutaneous drainage. The incidence and mortality of these infections has diminished greatly since the introduction of sulfonamides and antibiotics

Paradoxically enough, intercurrent infections, notably with measles, may be followed by improvement (p. 492).

In adults, after a varying number of years which may extend to decades, hypertension and impairment of renal function may develop and the patient succumb to uremia or some cardiac or cerebral manifestation of hypertension and arteriosclerosis As indicated above (p.465), this course results from glomerular hyalinization.

The cases occurring in the secondary stage of syphilis usually respond to antisyphilitic treatment, though it may take a long time before the protein disappears completely from the urine. There are cases of chronic nephrosis complicating secondary syphilis in which antiluetic treatment is of no avail In one such case reported by Dieulafoy, the edema persisted and death from erysipelas occurred on the forty-fifth day I have also seen a case of this kind in which antiluetic treatment did not help and when subcutaneous drainage was attempted, fatal erysipelas ensued.

THE TREATMENT OF CHRONIC NEPHROSIS

Apart from the now almost extinct syphilitic cases, there is no specific etiologic treatment for chronic nephrosis The main measures in use are:

1. Sodium restriction
2. Correction of protein starvation.
3. Intravenous infusion of plasma or serum albumin.

content of the diet and not to the concomitant sodium restriction. Theoretically, there are several ways in which augmenting the protein ration might help to reduce edema:

lema on high protein

However, Maclean[166]

high protein diet was

beneficial although there was no rise in plasma albumin. I have also seen many cases in which edema decreased greatly when the protein intake was elevated from a low level to 100 grams or more daily without concomitant change in the plasma albumin level. But in other patients increasing dietary protein is followed by gradual, though slow, rise in plasma albumin. In most of the cases in which there seemed to be definite correlation between elevation of protein intake and rise in plasma albumin, there has been previous protein deficit because of either poor appetite, gastro-intestinal disturbances or the prescription of a protein-poor diet. My impression is that, apart from such cases in which protein intake was previously very low, the plasma protein level in the nephrotic syndrome is primarily determined by the permeability of the kidney to protein, and that with massive proteinuria it is difficult, indeed often impossible, significantly

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albumin located outside of the blood vessels and changes in the level of one component of the "exchangeable albumin pool" are doubtless paralleled by alterations in the other.* And even when plasma albumin ascends *pari passu* with increase in protein intake, it is difficult to be sure that the rise is actually due to dietary change, fluctuations in plasma albumin level of obscure origin are common in the nephrotic syndrome even when dietary protein is constant. Despite this well established fact, there would

capacity to regenerate plasma proteins removed by plasmapheresis, such

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3. Epstein believes that another factor in the favorable effect of high protein diet is the specific dynamic action of the protein which, in his opinion, helps to counteract the occasionally low basal metabolic rate.

4. In individuals suffering from protein starvation as a result of proteinuria and/or low protein intake, increase in dietary protein may favorably affect anemia and general nutrition, and thereby, through mechanisms not clearly understood, combat edema.

but also the protein lost in the urine. Children also need ample protein for growth. As was seen above, the loss of highly differentiated plasma protein in the urine may amount to 20 or 30 grams a day over a period of months.

2. The concentration of albumin in the blood plasma is lowered in chronic nephrosi
probable that a
of the plasma proteins.

3. Chronic nephrosis is a disease which extends over months or years; restriction of protein for such long periods renders the patient weak, anemic and presumably more susceptible to the secondary infections that

Epstein broke completely with
. Following initial opposition, because of the traditional fear of both physicians and the laity of meat and other protein foods in "Bright's disease," Epstein's contention, that very considerable quantities of protein should be supplied the patient with chronic nephrosis, has been very widely accepted, though there is still a diminishing number of opponents, *e g*, Addis.[221] And in actual practice it seems quite clear that better results are obtained by giving the patients ample protein. This is often demonstrated when patients whose protein intake has previously been severely restricted are given an ample ration of protein; they regain strength, feel more hopeful, the anemia improves and the edema may decrease or even disappear. That these patients actually suffer from protein starvation seems to be shown by a careful metabolic study of cases of the nephrotic type of glomerulonephritis and chronic nephrosis by Peters and Bulger,[164] who find that "If they are given more than enough protein to replace the amount lost in the urine, they will store the excess within certain limits, thus repairing the effects of the previous nitrogen wastage" In one of their cases the storage lasted for almost three months. A similar retention of nitrogen has been observed by Peters and by Grabfield[165] to follow the administration of large quantities of crystalline urea to a nephrotic patient. Inasmuch as Grabfield found that the nitrogen retention was accompanied by sulphur retention and did not result in elevation of the non-protein nitrogen of the blood, he suggests the possibility that the nitrogen of the urea may be built up into deposit protein, to replace that which has been lost as a result of the proteinuria. If this interpretation is correct, and the evidence for it is at least very suggestive, it is of far-reaching general metabolic significance. Moreover, it would indicate that the administration of large quantities of urea to nephrotic patients is of value not only as a diuretic but also to help in the regeneration of the lost protein. However, further evidence is needed before this conclusion can be drawn

In former years, when most patients with edematous forms of Bright's disease were kept on a protein-poor diet, it was common to observe diuresis and disappearance of edema when an adequate protein ration was instituted. Nowadays, since the dangers of protein starvation in massive proteinuria are generally appreciated, it is exceptional to see striking benefit which can be unequivocally attributed to increasing the protein

Subsequent investigations showed that nothing is gained by raising the protein intake to very high levels. Peters and Bulger found that by the *administration* of large amounts of carbohydrate and fat to patients with the nephrotic syndrome, they reduce the daily protein *catabolism* to from 0.5 to 0.7 gram per kg. body weight. If this is done, a daily ration of ... a large surplus over the amount

...

of Peters and Bulger, Keutmann and Bassett found that, ... protein intake, increasing the caloric value of the diet by increments of ... the deposition of protein.

...

rations than adults However, Farr[177] found that even children fail to assimilate more than 3.3 grams of protein per kg body weight. His observations indicate that the optimum protein intake for nephrotic children is but little above that of the healthy child There seems to be no evidence that any advantage accrues from giving children with the nephrotic syndrome more than 2.5 grams of protein per kg. body weight.

The diet should contain sufficient carbohydrate and fat to give it a high caloric value and thereby decrease protein catabolism In general, the pat ...
ori ...
however, that the ...
influence the lipemia of chronic nephrosis This has been confirmed by Page and Farr[178]

Nor is there any evidence that the lipemia is harmful (apart from possibly

...

The most generally helpful diet in chronic nephrosis would thus seem to be one containing about 100 grams daily of protein and of high caloric content from both carbohydrate and fat. Sodium is restricted as much as is compatible with adequate protein intake Often, sodium-poor protein

...

these sources of energy may have to be restricted All the arts of the kitchen must be used to render the diet palatable or even tolerable to patients

5. There is still another mechanism, hitherto hardly considered, through which augmentation of the protein content of the diet may enhance diuresis, namely, *increase in blood flow through the kidneys*. Jolliffe and Smith[170] showed that in the dog urea clearance is greater on a high than on a low protein diet, and it has since been found in the same animal that glomerular filtration and renal blood flow are both accelerated by high protein diet (Van Slyke *et al.*,[171] Pitts[172]). While in man these differences seem not to be as great, there is also evidence that glomerular filtration and renal blood flow are both more rapid on a high protein diet than when dietary protein is low (White and Rolfe,[173] Pullman *et al.*[174]). That increased protein content of the diet calls forth greater renal work is shown by the hypertrophy that it produces in the rat's kidney (Addis[175]). These findings indicate that increase in dietary protein has a profound augmenting effect on renal blood flow and function, which may be important when diuresis is produced on such a diet.

It would appear that the relations between variations in the protein content of the diet and the urinary volume in nephrosis are complex and not well understood

Hypothetical objections may be raised to an ample protein diet in chronic nephrosis. In rats with experimental nephritis (p. 558) or subjected to ablations of large parts of the kidney (Addis[176]), it has been found that high protein diets may accelerate renal failure. And to the extent that increase in the protein content raises the plasma albumin level, there will be an increase in the proteinuria that may be damaging to the kidneys. But there is no evidence that either of these deleterious effects occurs in lipoid nephrosis

Before increasing the protein content of the diet, one must be certain that renal function is intact. Any evidence of impairment of renal excretory *function immediately contraindicates the high-protein diet*, although it does not militate against an adequate protein ration (*e. g.*, 50 grams plus the loss in the urine daily). The specific gravity of the urine should be watched carefully throughout the course of the disease. If the concentration test (p. 95) shows that the specific gravity can exceed 1.022, there need be no fear of serious nitrogen retention, even if the urinary volume is as small as 500 cc. daily Not uncommonly, there will be a rise in the urea nitrogen content of the blood to about 25 or 35 mg. per 100 cc. during the high-protein diet, but this need occasion no fear as long as the high specific gravity of the urine shows that renal function is good As Maclean, Peters and Bulger, and others have pointed out, there is no convincing evidence that moderate increase in the nonprotein nitrogen of the blood is in any way harmful.

The diet originally recommended by Epstein is as follows: Protein, 120 to 240 grams, fat, 20 to 40 grams, and carbohydrate, 150 to 300 grams, having an energy equivalent of from 1250 to 2500 calories He allows from 1200 to 1500 cc. of fluid daily and sufficient salt to make the diet palatable The articles of food used by Epstein are: lean veal, lean ham, whites of eggs, oysters, gelatin, lima beans, lentils, split peas, green peas, mushrooms, rice, oatmeal, bananas, skimmed milk, coffee, tea and cocoa.

shown by catheterization of the renal vein that renal blood flow is greatly increased and there is marked acceleration of glomerular filtration. However, decreased tubular reabsorption through endocrine mechanisms may also enter (Luetscher).

The diuresis from a single injection of even 50 or more grams of salt-poor albumin is transitory, and to obtain significant results the injection must be repeated a number of times. The diuresis usually stops soon after the termination of the injections; further continuation is probably due to an

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The value of salt-poor albumin in chronic nephrosis has not proved to be as great as originally hoped for. Usually, but by no means always, it is possible by repeated injections to reduce the edema considerably or even completely. But diuresis generally stops with cessation of the injections and the edema usually returns unless there is spontaneous remission. The chief benefit from salt-poor albumin is in extremely edematous patients who do not respond to other measures; in them, if a brief period can be tided over with the aid of albumin, spontaneous remission may set in or salt restriction or other treatment may maintain the improvement. No good purpose would seem to be served by administration of salt-poor albumin to patients with little or no edema; actually, in these circumstances little diuresis is usually produced. Salt-poor albumin is very dear and many patients have gone to unjustified expense where little benefit was to be anticipated. There is no reason to believe that administration of albumin has more than a temporary effect or that it alters the natural history of nephrosi

hypertension or re

blood volume will

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or fullness in the head during the injections.

Acacia.—Acacia is a colloid which leaves the blood stream but slowly and while there elevates the oncotic pressure of the plasma. It may still be found in the blood stream three years after injection. Used as a plasma

orld War I, it was introduced into

rtmann[151] and was later advocated

f acacia

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mann and

his associates observed good results when they administered this 30 per cent solution diluted with an equal volume of distilled water. In severe cases with nephrotic edema, the injection has to be repeated every three or four days to maintain an effective concentration in the plasma. They administered acacia to 6 patients with chronic nephrosis. In 5 of the 6 patients, diuresis was produced whenever sufficient acacia had been taken to bring the colloid osmotic pressure of the serum up to between 13 and 21 cm. of water. By continuing the administration long enough, they were

with poor appetites, but this can usually be accomplished. The technique of sodium restriction is discussed in Chapter 6.

Intravenous Infusion of Plasma and Serum Albumin.—Attempts were long ago made to elevate the lowered oncotic pressure of the plasma and repair the protein deficit of chronic nephrosis by transfusion of blood or plasma. Apart from improvement of anemic patients by blood transfusion, the results were doubtful and at best transitory; enough protein significantly to affect the enormous deficit could hardly be obtained from unconcentrated plasma. Much better results were gotten by Aldrich and his coworkers[179] by infusion of human blood serum concentrated five times by the lyophile process. In 6 of 9 children with chronic nephrosis, they observed immediate diuresis with clearing of edema followed the injection. The preparation of concentrated serum albumin during World War II by the Harvard Plasma Fractionation Laboratory, and especially of salt-poor albumin (Scatchard *et al.*[180]), offered a promising method for combating hypalbuminemia and protein deficiency in the nephrotic syndrome. Clinical trials of albumin in the nephrotic syndrome were soon made by Janeway,[181] Luetscher,[182] Thorn[183] and their associates, and it has since been widely used, though the great expense has been a drawback.

When albumin is injected intravenously into an individual with edema, the increased colloid osmotic pressure of the plasma draws remarkably large volumes of intercellular fluid into the blood stream.* Luetscher found that the injection of 50 grams of salt-poor albumin might be followed by a rise in plasma volume of as much as 50 to 100 per cent with visible venous distention and rise in venous pressure. The amount of the rise in plasma albumin concentration and oncotic pressure is largely determined [illegible] uid. The concentration [illegible] blood. Unfortunately, [illegible] produced by the injection is transitory, it is quickly distributed between the plasma and the extravascular compartment of the protein pool and much is lost in the urine. If the albumin level in the plasma is built up by repeated injections, the proportion of the injected albumin lost in the urine rises because of increased filtration. Luetscher found that at the end of two weeks after a course of albumin injections all the albumin given can be accounted for as excess albumin and nonprotein nitrogen in the urine.

Injection of albumin into an nephrotic patient with edema is followed by water diuresis of varying magnitude. In nonedematous individuals without a large volume of intercellular fluid available for osmotic mobilization, diuresis is slight or absent.** Luetscher found that when increased excretion of sodium is produced by injection of albumin, it follows the water diuresis; if no rise in sodium excretion occurs, water diuresis also stops. The mechanism of the diuresis is not entirely clear. Cargill[186] has

* According to the calculations of Scatchard, Batchelder and Brown,[184] each gram of albumin should hold about 18 cc. of fluid in the blood stream.

** In fact Petersdorf and Welt[185] found that in normals hyperoncotic solutions of albumin have an antidiuretic effect due to increased tubular reabsorption of water, which they regard as a passive consequence of enhanced reabsorption of sodium chloride in the proximal convoluted tubule.

to children and 300 mg. to adults. There seems to be no advantage in increasing the dose and it may be that smaller amounts are equally effective. Inasmuch as diuresis is most apt to appear to occur after cessation of cortisone or ACTH, even as long as four days after, the hormone should be given in a course which is terminated abruptly without tapering off. There appears to be no greater likelihood of obtaining a satisfactory response by prolonging the course to more than ten days. If the result is unsatisfactory, a second course may be given after five days. Sometimes, diuresis is first obtained after a second or even third course. Diuresis may be produced during repeated courses.

Recently, Lange[199] and his associates have obtained remissions of longer duration by intermittent administration of ACTH or ACTH followed by cortisone. They gave 6 children with the nephrotic syndrome 100 mg. of ACTH daily for seven days; diuresis occurred in all between the ninth and twelfth days. This was followed by 100 mg. of ACTH daily for three consecutive days for the next five to eight weeks. Only transitory relapse of edema occurred in 1

to twenty-six months

cortisone (100 mg q.i ... consecutive days for the interrupted treatment after the initial ACTH course. This interrupted method of treatment has ... t.

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hormone, ... during the first days by retention of sodium, chloride and water with resultant increase in edema and weight; during this period there is often increase in proteinuria and perhaps in lipemia. The urinary volume may then increase while the hormone is still being given. However, if a response is obtained at all, the more frequent sequence is for diuresis to set in one to three days after ACTH or cortisone has been stopp ... at a high level for several days ur ... . At the same time proteinuria may ... albumin

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of such long term treatment have yet to be evaluated against possible benefits. With small maintenance doses of cortisone (37.5 daily) over long periods, Riley had relapses in 10 of 12 nephrotic children.

Little definite is known concerning the mechanism of action of cortisone and ACTH in the nephrotic syndrome ...

... peak about the eighth or ninth day ... cortisone or ACTH therapy, reaching ... Correspondingly, Selye's[202]

able completely to rid their patients of edema. When the first injection failed, a second one given within a day or two produced striking results. Landis advised that, after a test dose of 5 or 10 grams, acacia should be administered by slow intravenous injection in daily amount of 20 to 30 grams until 120 to 180 grams have been given. Using this technique, he obtained good diuresis in 5 of 6 patients with nephrotic edema. Because of the danger of severe reactions with chills and circulatory collapse with large doses, which I have seen repeatedly, such divided dosage is to be preferred. Austin and McGuinness[190] observed dangerous rise in blood volume following a large injection. I obtained excellent diuresis in several patients with nephrotic edema by the injection of acacia, but in others it failed. Mercurials, previously unsuccessful, may produce diuresis after the colloid osmotic pressure of the plasma has been raised by acacia.

In addition to the acute reactions just mentioned, acacia has another undersirable by-effect: it is deposited in large quantities in the liver cells, where it may remain for long periods. Yuile and Knutti[191] showed experimentally that the administration of acacia produces chronic hypoproteinemia. It appears that the deposition of acacia in the liver inhibits the formation of plasma proteins in this organ. For this reason acacia has been almost abandoned in recent years, I have not given it in several years.

The recently developed plasma expander, *dextran*, has also been tried in the treatment of nephrotic edema. Wallenius[228] found that each intravenous injection increased the urinary volume in the nephrotic syndrome by at least 400 cc. Olive[229] *et al.* administered a 10 per cent salt-free solution of dextran to 12 children with nephrotic edema in doses averaging 1.43 gm. per kilogram body weight. Diuresis was produced but the effects were temporary.

Cortisone and ACTH.—In some patients with the nephrotic syndrome, remarkable diuresis and regression of edema is produced by ACTH or cortisone. Clinical remission with disappearance of edema, diminution or rarely even disappearance of proteinuria, rise in plasma albumin and fall in plasma lipids may occur. Diuresis is produced more often than diminution in proteinuria and may occur in the absence of the latter or significant change in plasma albumin level (Luetscher,[227] own observations) Usually, the remission is of brief duration, but it may last for months or in rare instances exceed a year That hormonal therapy *per se* results in cure of chronic nephrosis has not been demonstrated. Luetscher[192] observed diuresis from cortisone in 6 of 11 patients with the nephrotic syndrome. Reports by Farnsworth and Dupee,[193] Luetscher,[194] Metcoff,[195] Spector,[197] Riley[196] and Rapoport[198] *et al.* indicate that corticotropin produces diuresis in one or more courses in about two-thirds of nephrotic patients In my experience the proportion has been even higher in the first trial in young children but lower in adults. In the cases personally observed, ACTH has proved more frequently effective and has produced a more profuse diuresis than has cortisone. However, Riley found both agents equally effective.

In adults 75 to 100 mg daily of ACTH may be given intramuscularly or a correspondingly smaller amount intravenously; in young children about 50 mg. daily is a usual dose About 200 mg daily of cortisone may be given

... nephrotic form of glomerulonephritis ...

2 children with lipoid nep... the 3 children with glomer... the other relapsed after three and half months. The 3 children with glomerulonephritis had only transient improvement. When nephrotic children develop measles, there may be aggravation of the nephrotic syndrome in the pre-eruptive stage with diuresis when the rash is florid. Remission induced by measles may be complete, with disappearance of proteinuria and edema and return of the plasma proteins and lipids to normal. Unfortunately, the remission generally proves transient; when this is not the case, the possibility exists that ... has been spontaneous cure. While the mechanism of improvement ... the remissions induced by ... may include hypersecretion of corticotropin ... by other ... six month ... remission following homologous serum jaundice.

Because of the observations of remission following measles, the disease has been induced for therapeutic ... inoculation Janeway[181] inoculated ... ay carried out the inoculation by nasal instillation of throat washings from patients with Koplik spots, which were treated with several hundred thousand units of penicillin and stored at minus 70° C. Patients inoculated with measles should be given penicillin as a prophylactic of secondary infections.

The remission of chronic nephrosis by measles seems to be akin to that resulting from ACTH. For this reason, and since the child may be very sick with measles, induction of the disease for therapeutic purposes does not now seem advisable.

Thyroid Extract.—This has been extensively used in the treatment of chronic nephrosis ...

therapeutic result from the administration of thyroid in a case of chronic nephrosis.

Large doses of thyroid and thyroxin were, however, first used extensively in the treatment of chronic nephrosis by Epstein, from whose work dates the formerly wide utilization of thyroid treatment in chronic nephrosis. He was led to its use by his observations of lower basal metabolism in many cases and by other analogies between the clinical pictures of myxedema and chronic nephrosis. Epstein found that patients with chronic nephrosis have enormous tolerance for thyroid, rarely manifesting any toxic symptoms or notable elevation in the basal metabolic rate as long

animal experiments revealed that large doses of ACTH produce dilatation and hyperemia of the glomerular loops. Increase in PAH clearance and other evidences of improved tubular function have been observed by Metcoff *et al.* Luetscher[203] found a decrease in the previously high urinary excretion of salt-retaining corticoids during diuresis from either cortisone or ACTH. It appears that the respective roles of increased glomerular filtration and tubular rejection of water and salt in the diuresis induced by cortisone or ACTH have not yet been assessed.

At present, the use of ACTH or cortisone constitutes the most valuable therapeutic measure available for treatment of the nephrotic syndrome, even though it is not yet proved that the hormones influence the fundamental course of the disease. They should be tried in patients who do not respond to salt restriction and high protein diet. In the presence of massive edema not evacuated by other measures, ACTH or cortisone may be tried despite *slight* hypertension or azotemia, and may produce diuresis However, they should be used very cautiously under these circumstances and stopped if there is any rise in blood pressure or azotemia. With marked hypertension the hormones should not be used for they may dangerously or even fatally aggravate the hypertension. I have seen three patients with renal disease (two with glomerulonephritis and one who apparently had renal involvement in scleroderma) in whom the administration of ACTH was followed by dangerous hypertension; none of these, however, had a nephrotic syndrome In view of the lowered resistance of the nephrotic patient to infection, it is probably wise to accompany the hormone by penicillin if there is active infection, because it is possible that ACTH or cortisone may lower resistance, the doses of the antibiotic should be large. Metcoff *et al.* mention three deaths in children with the nephrotic syndrome during treatment with ACTH (hypertension with hypotonicity and convulsions, and overwhelming infections) which seemed to be related to the treatment. Orange juice and/or potassium salts should be given to prevent hypokalemia and metabolic alkalosis. Acne, hirsutism, moon face, etc , may occur during treatment but quickly pass away and are not deterrents. Slight elevation of blood pressure is not rare. I have seen 2 instances of massive hemorrhage from one adrenal gland during ACTH treatment for the nephrotic syndrome, the first case was subjected to laparotomy because an acute abdominal catastrophy was suspected During the diuretic phase, sodium or/and potassium depletion may occur and require administration of the appropriate ion. Contrariwise, Luetscher[225] points out that in early days of treatment marked hyperkalemia may occur.

Infection With Measles.—It was long ago observed that patients, especially children, with chronic nephrosis may have profuse diuresis following an intercurrent infection, notably measles. Debré[204] and his associates reported a case of nephrosis of four years' duration in which measles was followed by remission of at least four months. They collected 15 other cases with remission due to measles, which was permanent in 2. Rosenblum *et al.*[205] studied 7 children with the nephrotic syndrome who contracted measles during an epidemic. Three had protracted and 3 permanent improvement. Blumberg and Cassady[206] observed 2 children

the other relapsed after three and half months. When nephrotic children had only transient improvement. the nephrotic syndrome in

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Thyroid Extract —This has been extensively used in the treatment of chronic nephrosis.

Eppinger[208] found that the resorption of salt solution from the subcutaneous tissues is slower than normal in the thyroidectomized animal. He was able to accelerate greatly the resorption of the salt solution by the administration of thyroid extract. In several instances of edema of obscure nature which had resisted other measures, Eppinger induced diuresis and cleared up the edema by thyroid therapy. Volhard[209] observed an excellent therapeutic result from the administration of thyroid in a case of chronic nephrosis.

Large doses of thyroid and thyroxin were, however, first used extensively in the treatment of chronic nephrosis by Epstein, from whose work dates the formerly wide utilization of thyroid treatment in chronic nephrosis. He was led to its use by his observations of lower basal metabolism in many cases and by other analogies between the clinical pictures of myxedema and chronic nephrosis. Epstein found that patients with chronic nephrosis have enormous tolerance for thyroid, rarely manifesting any toxic symptoms or notable elevation in the basal metabolic rate as long

as the lipemia is present. He observed that in many instances of chronic nephrosis, the use of thyroid extract diminishes the proteinuria, produces diuresis with reduction in the edema, and reduces the lipemia. In Epstein's opinion, these beneficial results are due to stimulation of protein metabolism, and abnormality of which he regards as the fundamental basis of the disease. Epstein uses thyroid therapy purely as an adjuvant to his high-protein diet, both serving to increase the utilization of protein. Another factor that might be concerned when thyroid therapy is effective in chronic nephrosis is the increase in colloid osmotic pressure of the plasma proteins which Malkin[210] reported after the administration of thyroid; this observation has not been confirmed and seems improbable.

✓Epstein starts with small doses of thyroid extract (0.5 to 1 grain three times daily) and then increases until 15 grains a day is reached. In some cases he has given much larger doses or used thyroxin intravenously (5 to 10 mg., repeated in a week). He has found that toxic symptoms do not develop as long as hypercholesteremia is present, and uses this as a guide for the dosage. In some instances he has persisted in thyroid treatment for over a year

✓While diuresis occasionally follows the administration of thyroid, much more often there is little or none. When definite diuresis does occur, it is difficult to exclude spontaneous fluctuations in the disease And theoretically the advisability of accelerating protein metabolism in a disease characterized by protein depletion seems dubious. The lowered basal metabolic rate, when present after allowance for edema, may be an adaptation to the protein deficiency. The writer has not used thyroid in the nephrotic syndrome in several years apart from rare instances in which there seemed to be good evidence of hypothyroidism.

Diuretics.—*Mercurial diuretics* sometimes produce copious diuresis in the nephrotic syndrome. This is more apt to occur after preparation with ammonium chloride or another acid-producing salt (p. 190) However, the mercurials are often totally ineffective in chronic nephrosis, and when they are diuretic their efficiency generally decreases with successive injections It is rare to be able to control the edema of a severely hypoproteinemic patient with mercurials. There seems to be little danger in chronic nephrosis from the cautious probatory use of mercurials by subcutaneous or intramuscular injection. Saxl and Becker[211] found that the injection of salyrgan diminishes the quantity of protein in the urine in chronic nephrosis. However, I have seen augmented proteinuria and the appearance of red cells in the sediment following use of a mercurial in nephrosis. If the first injection of a mercurial to a patient prepared with ammonium chloride does not produce diuresis, it does not seem to be worth while to continue with the injections

Urea is a diuretic which is exceptionally helpful in controlling edema for months or even years Urea must be given in large doses (60 to 90 grams daily or even more in 50 per cent solution in syrup or in capsules). The disagreeable taste, nausea, vomiting or diarrhea often necessitate discontinuance.

Purine diuretics are usually useless from the start or soon lose any effectiveness they may initially display.

The use of large doses of *sodium and potassium* salts in chronic nephrosis has been mentioned above (p. 483).

... are occasionally a valuable adjuvant

up to one year My results have not ... few cases use of a resin has delivered edema. If there is impairment of renal function documented by hyposthenuria, a cation exchange resin should be administered only with great circumspection; there is much danger of acidosis due to base depletion and sometimes hypokalemia develops After a few days, potassium chloride should be given. There is great difficulty in getting children (and many adults) to take a resin Cation exchange resins should not be given to patients with azotemia because the likelihood of help is slight and the dangers of acidosis and hypokalemia great

Other Measures.—*Infectious foci* should be removed or drained, but one should be cautious in predicting good results from the operation. In adults I have seen no striking, if any, benefit from removal of tonsils, drainage of sin... etc. In view of the good results obtained by pediatricians by dra...
these should be ...
in my experience ... procedures has been decidedly exceptional. Nowadays, treatment of sinus infection in nephrotic patients with other than by antibiotics is rarely called for

On the basis of the rare instances in which improvement follows febrile infections (p 492), treatment by *injections of foreign protein* has been tried, but generally with little success Clément[213] reported cure of chronic ...

with the diuresis following ACTH, injection of the latter is more effective and certainly less trying to the patient.

Mechanical removal of edema may be necessary. Extensive effusions into serous cavities should be tapped if they cause dyspnea or other symptoms that do not respond to diuretic measures Salt restriction may be more effective after tapping ascites It is best to avoid drainage of the subcutaneous edema because of the extreme susceptibility of these patients to infection, but in rare instances it becomes necessary and penicillin has almost eliminated the formerly great danger of erysipelas or cellulitis.

Decapsulation has been recommended in chronic nephrosis. Oehlecker[214] reported 2 cases in which this operation was followed by marked improvement In view of the fluctuating course of so many of these cases, it appears to me difficult to evaluate the benefit of the operation. There appears to be no ...

General Care.— ...
bed may present ...
there is no altern...
up and about, despite increase of the edema of the legs toward evening, there seems to be no good reason for enforcing bed rest Small children are

best allowed to play throughout the home, and in mild weather outdoors, despite considerable edema and ascites. The improved appetite while up and about facilitates adequate diet. Many patients with proteinuria and low grade edema are able to pursue an occupation even though the feet swell more as the day goes on. Of course every effort is to be made to avoid respiratory infections and protect children from contagion. If circumstances permit, and dietary control is possible, nephrotic patients may prefer to pass the winter in the South, where they can be outdoors and the changes of respiratory infection are less. But climatic treatment has no remarkable virtues in chronic nephrosis, and a family should not be permitted to ruin themselves financially in order to obtain it.

Antiluetic Treatment.—In syphilitic nephrosis antiluetic treatment should be given and usually is curative. Formerly mercury or bismuth (Felber) were the usual initial drugs, followed by arsenicals. Overly energetic treatment with these drugs was observed to provoke Herxheimer reactions with anuria, increasing azotemia, edema and uremia (Moore[215]). At present penicillin is the drug of choice (Tucker[216]).

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Chapter

17

DIABETIC GLOMERULOSCLEROSIS

as the great menace ... In 1917 shortly before the insulin era, Joslin ...

... ment is bringing about they will deserve attention. ... of the kidneys in diabetes differs from that in the heart, extremities and other organs in that it is the result not only of arteriosclerotic ischemia, but also includes a remarkable lesion in the glomerular tufts, of which the analogue in other organs (except perhaps the retina) has not yet been described

The attention of the pro ...
lesions of diabetes by the ...
1936 In 8 necropsies, in ...
observed char ...
believed these ...
tissue in the ... *glomerulosclerosis* There was also lipoidosis of the tubules and intertubular tissue They found that the clinical picture of patients presenting ...

often been referred to as the ...

More recent observations indicate that the characteristic glomerular ... the ... the ... is of the renal disease. The process is an intrinsic part of the widespread "degeneration" of the vessels in diabetes. The designation *intercapillary* ...

... and Wilson occur so frequently* on every medical service that many physicians must, like the writer, have chided themselves for failure to discern their correlation with diabetes. The frequency with which glomerulosclerosis develops in long-standing diabetes is now familiar to all intern-

* On the Medical Service of Beth Israel Hospital, where the proportion of diabetics tends to be high for an acute general hospital, in recent years there have been more cases of diabetic glomerulosclerosis than of glomerulonephritis.

ists. Nevertheless, doubts have been expressed regarding the *specifically diabetic* causation of the renal lesions; in fact, Kimmelstiel and Wilson originally regarded them as merely an intensification of a sclerotic process that commonly develops in the kidneys of the aged in the absence of diabetes. Horn and Smetana[3] claim to have found the same renal changes more often in nondiabetics than in diabetics, although they observed the far advanced lesions only in diabetics. Recent careful anatomic studies by Siegal and Allen[4] and Bell[5] have shown that the typical large spheroidal hyaline nodules in the glomeruli are almost, but not absolutely pathognomonic for diabetes; Siegal and Allen and Bell each mention a single exception in a nondiabetic and I recall very rare instances in which globular hyaline lesions were seen in the glomeruli of arteriolosclerotic kidneys where there was no evidence of diabetes. But the rarity of such exceptions should be stressed. Moreover, if the full-blown clinical picture—diabetes, hypertension, marked proteinuria, nephrotic edema, azotemia, and above all diabetic retinopathy—is present, one can confidently predict that the hyaline glomerular lesions will be found. In aglycosuric cases, mild diabetes is sometimes detected as a result of sugar tolerance tests instigated by the presence of some of the clinical manifestations just enumerated.

Occurrence.—Glomerulosclerosis is a common development in present-day diabetics. In fact, Laipply[6] *et al* detected the lesion at post-mortem in a higher proportion of diabetics than had hyalinization of the islets of Langerhans Allen observed the lesion in one-third of diabetics over forty. Henderson[7] *et al.* found glomerulosclerosis in 61 of 313 autopsies on diabetics. From a survey of the available statistics, Kimmelstiel and Porter[8] conclude that glomerulosclerosis occurs in about 17 per cent of all diabetics, twice as often in women as in men. The peak incidence is in the sixth decade. It is extremely rare in the young; Kimmelstiel and Porter found only 3 cases before the age of twenty. The large majority occur in mild diabetics; often, as mentioned above, the diabetes is discovered only after other manifestations of glomerulosclerosis have developed. There is considerable correlation between the duration of diabetes and the incidence of glomerulosclerosis. Henderson *et al.* found that in their cases with nodular renal lesions the average known duration of diabetes was 11.2 years. That diabetic glomerulosclerosis may develop in less than four years is shown by Derow and Schlesinger's[9] observation of advanced lesions in a diabetic of 8 years duration in whom nephrectomy four years before death for suspected neoplasm had shown no changes

PATHOLOGICAL ANATOMY

The kidneys may be of normal size or somewhat enlarged Diabetic glomerulosclerosis *per se* apparently does not lead to contracted kidneys. The gross appearance, notably the presence or absence of granulation, is largely determined by associated arterio- or arteriolosclerosis. In the exceptional cases in which the hypertension has entered the malignant phase with arteriolar necrosis, there may be hemorrhages. The deposition of lipid is often evident in the cut section.

are in the *glomeruli*. They
spherical or oval shape. The
ule. The spherules vary from
... appear quite

hyaline ...
the appearance of being located between the ca...

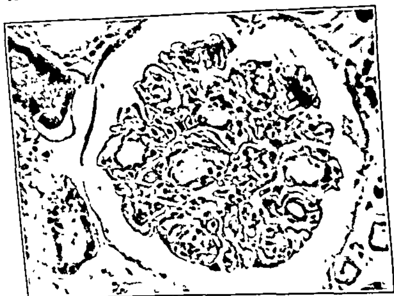


FIG. 17 —Characteristic nodular lesions of diabetic glomerulosclerosis in a diabetic of many years standing who succumbed to ascending cholangitis (NPN 65 mg per cent ten days before death)

which reason Kimmelstiel and Wilson originally coined the term intercapillary glomerulosclerosis More recent histological observations by Allen and Bell indicate that the hyaline masses originate in localized thickening of the capillary wall, according to Bell there is thickening, splitting and fusion of the inner capillary basement membranes Using the periodic acid-Schiff staining technique, which sharply delimits the basement membrane, Rinehart[31] *et al.* likewise find that the lesion is initiated as a thickening of the endothelial component of the basement membrane

The nodules just described are not the only alterations in the Malpighian tufts of diabetics More common is a widespread, nonnodular hyalinization of similar staining characteristics Bell has termed this the *diffuse* type of

diabetic glomerular lesion. The diffuse changes are always to be found when the nodular lesions are present, but often occur in the absence of the latter. The diffuse and nodular lesions are doubtless morphologic variants of the same process; the nodular lesions represent an advanced stage.

The nature of the hyaline deposit in the nodules and diffuse lesions is not known. In appearance they closely simulate amyloid, but specific amyloid stains are negative. Lipid stains also are negative apart from occasional minute droplets scattered in the large hyaline mass. Presumably the hyaline is largely protein, but Allen found it highly resistant to tryptic digestion. With the Mallory-Heidenhain stain, Allen observed that the hyaline nodules generally take the deep blue of collagen but that incompletely collagenized foci stain pink or purple orange. The hyaline stains pale yellow with Van Gieson.



FIG 18 — Another section from the same kidney as Figure 17, showing the marked arteriolosclerosis

But these are so exceptional that a histological diagnosis of diabetes can be ventured with a high degree of confidence when the typical glomerular nodules are seen. Nodular lesions in glomerulonephritis are accompanied by diffuse changes in the glomeruli which reveal their nature. In the rare instances in which typical isolated nodular lesions are seen without a clinical history of diabetes, the possibility exists that sugar tolerance tests would have revealed the disturbance of carbohydrate metabolism; it is just the mild forms of diabetes that furnish the main contingent of the Kimmelstiel-Wilson syndrome. While the diffuse hyalinization described

In kidneys the seat of the glomer... of the afferent arterioles. almost invariably marked hyaline thickening ... pronounced hyalinization. Though The efferent art... the thickening ... it is often of a deg...

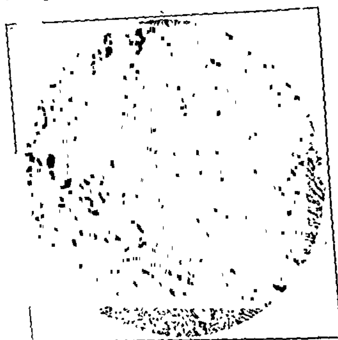


Fig 19 —Armanni-Ebstein cells in the tubules of the kidney in diabetes mellitus The bodies of the cells, which were filled with glycogen during life, are practically unstained, so that the cell border is very sharp

marked hyalinization of the vasa efferentia should awaken the suspicion of diabetes While arteriolar sclerosis is almost always found in diabetic glomerulosclerosis, it is not the cause of the latter. For one thing, there are rare instances of diabetic glomerular lesions without notable arteriolar sclerosis, this was true in a sixteen-year-old girl with severe diabetes of ten years' duration studied by Lapply *et al.* And one often sees spherical lesions in an individual glomerulus with little hyalinization of the appertaining arterioles Thickening and elastosis of the interlobular arterioles are common.

The *tubules* often exhibit considerable changes, though these are not specific. There is usually cloudy swelling and deposition of lipid in the

basal portion of the epithelial cells, most marked in the proximal convoluted tubules. Both isotropic lipids and cholesterol esters may be found. The deposition of lipid in the tubular epithelia is probably a storage phenomenon resulting from reabsorption of lipids from the glomerular filtrate, into which they penetrate as a result of increased permeability of the diseased glomerular loops to the frequently lipemic plasma. Casts and desquamated epithelia are often seen in the tubular lumens. There may be foci of tubular atrophy with replacement fibrosis; in these areas lipids are often demonstrable.

Glycogen Vacuolization.—In the pre-insulin days it was common to find in the kidneys of diabetics dying in acidotic coma extensive deposition of glycogen in certain parts of the urinary tubule. This deposition produces the large, clear cells known as Armanni-Ebstein cells, in which the cytoplasm appears almost unstained in the hematoxylin-eosin preparation and stains red with Best's carmine. The deposition of glycogen is generally described as occurring in Henle's loop, but Baehr[10] showed that the cells involved are those of that portion of the tubule which connects the proximal

enon of storage in some way connected with the hyperglycemia and glycosuria. The glycogen is presumably polymerized from glucose reabsorbed from the glomerular filtrate (*cf.* Oliver[11]). There is no evidence that the storage of glycogen in the renal cells produces clinical manifestations. Since the introduction of insulin, Armanni-Ebstein cells are very rarely seen.

Atherosclerosis of great ... al artery and its large and small branches ... Hall[29] observed it in all of 8 cases of the ... hich succumbed to uremia and believes that it played an important part in the widespread glomerular obliteration present in these cases.

NATURE OF DIABETIC GLOMERULOSCLEROSIS

Since the cause of diabetes is unknown and its basic nature obscure—the widely held theory of primary disease of the islets of Langerhans has great weakness (*cf.* Mirsky[12])—it is not surprising that even less is known of the pathogenesis of glomerulosclerosis However, several correlations seem relevant:

1. The development of glomerulosclerosis is correlated with the duration of the diabetes and not with the severity of the disturbance in carbohydrate metabolism as measured by the amount of insulin needed for control.

2. With only the rarest exceptions, intercapillary glomerulosclerosis is associated with arteriolar sclerosis in the kidneys.

3. In every necropsy that reveals intercapillary glomerulosclerosis, widespread arteriosclerosis is found, of a severity far beyond that correspondin

4. If

losclero

olger.[13] In 200
ot one escaped
veloped retino-
pathy exhibited proteinuria and hypertension at the time of the earliest retinal hemorrhage.

5 It does not appear to be proved that control of the disturbance in carbohydrate metabolism by diet and insulin lessens the incidence or postpones the onset of glomerulosclerosis. And in patients who already have evidences of glomerulosclerosis, the writer has seen no evidence that as good dietary and insulin control of the abnormality in carbohydrate metabolism as is feasible retards the progression of the renal disease.

6. In a dog which Lukens and Dohan[14] kept diabetic for five years by injections of pituitary extract, they observed hyaline lesions in the glomer-

1

arteriosclerosis and arteriolosclerosis, and the retinopathy—is an intrinsic component of diabetes It usually first becomes manifest long after the decreased sugar tolerance but ultimately reaches a demonstrable stage in the vast majority of cases of sufficiently long duration Glomerulosclerosis appears to be the analogue in the glomerular capillaries of the arteriosclerosis, artiolosclerosis, and retinal capillary aneurysms and phlebosclerosis (p 512) in other categories of vessels, which likewise ultimately afflict practically all long-standing diabetics, these changes often parallel one another and presumably have pathogenetic factors in common Contemporary thinking generally has assumed that these widespread vascular lesions in diabetes are consequences of a primary disturbance in carbohydrate metabolism, but this is not proved (*cf.* Mirsky and Dolger).

CLINICAL PICTURE

Diabetic glomerulosclerosis presents itself under many guises. Manifestations correlated with diabetes—the glomerulosclerosis, arteriosclerotic disease in the heart, extremities, brain or other organs, and diabetic retinopathy and neuropathy—are variously commingled, any may predominate Most often the symptoms of glomerulosclerosis appear in an individual known to have had diabetes, usually mild, for years; less commonly, glomerulosclerosis leads to discovery of previously unknown diabetes Remarkably enough, diabetes often becomes milder as the Kimmelstiel-Wilson syndrome evolves with a lessening in insulin requirement, and patients with the full-blown clinical picture of diabetic glom... ...osis

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basal portion of the epithelial cells, most marked in the proximal convoluted tubules. Both isotropic lipids and cholesterol esters may be found. The deposition of lipid in the tubular epithelia is probably a storage phenomenon

ular loops to the frequently lipemic plasma. Casts and desquamated epithelia are often seen in the tubular lumens. There may be foci of tubular atrophy with replacement fibrosis; in these areas lipids are often demonstrable.

Glycogen Vacuolization.—In the pre-insulin days it was common to find in the kidneys of diabetics dying in acidotic coma extensive deposition of glycogen in certain parts of the urinary tubule. This deposition produces the large, clear cells known as Armanni-Ebstein cells, in which the cytoplasm appears almost unstained in the hematoxylin-eosin preparation and stains red with Best's carmine. The deposition of glycogen is generally described as occurring in Henle's loop, but Baehr[10] showed that the cells involved are those of that portion of the tubule which connects the proximal convoluted tubule with Henle's loop. Glycogen may also be present in the epithelial cells and lumen of Bowman's capsule. The appearance of glycogen is not to be regarded as a degenerative change but rather as a phenomenon of storage in some way connected with the hyperglycemia and glycosuria. The glycogen is presumably polymerized from glucose reabsorbed from the glomerular filtrate (*cf.* Oliver[11]). There is no evidence that the storage of glycogen in the renal cells produces clinical manifestations. Since the introduction of insulin, Armanni-Ebstein cells are very rarely seen.

Atherosclerosis of great severity is common in the renal artery and its large and small branches in diabetic glomerulosclerosis; Hall[29] observed it in all of 8 cases of the Kimmelstiel-Wilson syndrome which succumbed to uremia and believes that it played an important part in the widespread glomerular obliteration present in these cases

NATURE OF DIABETIC GLOMERULOSCLEROSIS

Since the cause of diabetes is unknown and its basic nature obscure—the widely held theory of primary disease of the islets of Langerhans has great weakness (*cf.* Mirsky[12])—it is not surprising that even less is known of the pathogenesis of glomerulosclerosis. However, several correlations seem relevant:

1 The development of glomerulosclerosis is correlated with the duration of the diabetes and not with the severity of the disturbance in carbohydrate metabolism as measured by the amount of insulin needed for control

2. With only the rarest exceptions, intercapillary glomerulosclerosis is associated with arteriolar sclerosis in the kidneys.

3. In every necropsy that reveals intercapillary glomerulosclerosis, widespread arteriosclerosis is found, of a severity far beyond that corre-
spon[illegible]

4. [illegible]

loscle[illegible]

tributes

and Page

that in glomerulonephritis glomerular filtration and ... diminished with an elevated filtration fraction, and tubular excretory capacity was diminished. Hogeman[18] likewise observed decreased blood ... but found a diminished filtration fraction. Studies

from the anatomical findings.

With azotemia, *anemia* usually develops. It is of the same character as the anemia found in other forms of renal insufficiency.

Edema.—In exceptional instances, swelling of the feet is the first indication that glomerulosclerosis is developing. Most often, however, edema is ... festation if it appears at all. The edema may be either nephrotic ... heart ... c syn- ... sion of

not directly due to the diabetes is shown by its persistence despite a normal blood sugar level and absence of ketosis as a result of insulin control. Following diabetic patients over many years, Mann[20] *et al.* found that coincident with the development of clinical manifestations of glomerulosclerosis, the serum cholesterol rose above normal in 19 of 20 instances. As in other forms of the nephrotic syndrome, Mann observed that the rise in cholesterol correlated well with the fall in serum albumin.

Arteriosclerotic Complications.—Almost every patient with diabetic glomerulosclerosis sooner or later has symptoms due to arteriosclerosis Most common and important is coronary disease which often leads to heart failure and/or angina pectoris Coronary thrombosis is an ever-present danger and terminates some of the cases. There may be symptoms due to

Diabetic Retinopathy —Most, though *not all*, patients with glomerulosclerosis sooner or later exhibit retinal lesions They may be of three varieties (apart from the now almost extinct lipemia retinalis):

1 Hypertensive retinopathy (p 368)

2 Arteriosclerotic retinopathy (p 382).

3 Specific diabetic retinopathy This process is part and parcel of the diabetes itself and often so characteristic as to enable the ophthalmoscopic

... sions in diabetes, specific ... Combinations of two or three ... found specific ... ved advanced ... in diabetics ... It is there-

The Urine.—Proteinuria occurs in all the clinically recognizable cases and may long be the only sign. Often it is slight or intermittent when first detected. In most patients the proteinuria becomes more pronounced and as a rule becomes sufficiently massive to deplete the plasma albumin. The daily urine may contain more than 10 grams of protein.

The proteinuria is accompanied by hyaline and granular casts in varying number. Rifkin[16] and his collaborators have laid especial stress on the presence in the urinary sediment of doubly refractile lipids. These occur in cells, in casts or as free droplets. Rifkin *et al.* detected anisotropic lipids in the sediment in 39 of their 44 patients. They may be found only after careful search of several specimens or they may be abundant. Details regarding the detection of doubly refractile bodies will be found in the paper of Rifkin *et al.*; they state that the anisotropic particles are found chiefly in fresh acid urine. It should be remembered that cholesterol esters may be found in the sediment in all types of the nephrotic syndrome, including chronic nephrosis, glomerulonephritis and amyloidosis. However, careful search by Rifkin and his associates did not reveal them in 30 patients with "hypertensive vascular disease" without diabetes. Red cells are rarely prominent in the sediment of diabetic glomerulosclerosis; Rifkin *et al.* found none in 58 per cent of their patients and only 1 to 5 per high power field in the remainder. However, I have several times seen more numerous red cells in diabetic glomerulosclerosis, and gross hematuria may occur in the rare instances in which the hypertension enters the malignant phase.

The Blood Pressure.—Hypertension is a common but not constant manifestation of diabetic glomerulosclerosis. When a diabetic develops the proteinuria which subsequent observation proves to have been the initial sign of intercapillary glomerulosclerosis, the blood pressure is often normal and may remain so for years. But sooner or later, in most cases, the blood pressu [illegible] 67 per cent, [illegible] In the experi[illegible] course and do not have a myocardial infarction, hypertension develops in almost all. It may be moderate or pronounced and rarely is so severe as to produce the clinical picture of malignant hypertension. Usually the concomitant arteriosclerotic loss of elasticity of the aorta and other large vessels leads to proportionately greater systolic than diastolic hypertension. Often there is marked systolic hypertension without definite rise in the diastolic tension. The relatively lesser elevation of the diastolic (and mean) pressure is perhaps a factor in the rarity of malignant hypertension.

Renal Function.—In most of the cases renal function sooner or later becomes impaired. This is documented by hyposthenuria and azotemia. The latter may be present when kidney disease is first suspected or appear only after years of proteinuria. The rate of progression of the renal insufficiency may be slow and the patient survive for even two or three years after azotemia is first detected. Many of the patients die in uremia. Often the terminal picture is that of combined cardiac and renal insufficiency. The renal failure is usually due to both the specific glomerular lesions and arteriolosclerotic changes, and heart failure often also con-

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With azotemia, *anemia* usually develops. It is of the same character as the anemia found in other forms of renal insufficiency.

Edema.—In exceptional instances, swelling of the feet is the first indication that glomerulosclerosis is developing. Most often, however, edema is a late manifestation, if it appears at all. The edema may be either nephrotic or cardiac in origin, perhaps most often both hypoproteinemia and heart f causation There may be a classical nephrotic syn- inversion of

. it the hyper-cholesterolemia in such cases is actually part of a nephrotic syndrome and not directly due to the diabetes is shown by its persistence despite a normal blood sugar level and absence of ketosis as a result of insulin control. Following diabetic patients over many years, Mann[20] *et al.* found that involvement of clinical manifestations of glomeru-

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Arteriosclerotic Complications.—Almost every patient with glomerulosclerosis sooner or later has symptoms due to arteriosclerosis. Most common and important is coronary disease which often leads to heart failure and/or angina pectoris. Coronary thrombosis is an ever-present danger and terminates some of the cases. There may be symptoms due to arteriosclerosis of the lower extremities or brain. In a high proportion of patients with diabetic glomerulosclerosis, the clinical picture is dominated by coronary or other arteriosclerotic complications

Diabetic Retinopathy.—Most, though not all, patients with glomerulo- e of three

3 Specific diabetic retinopathy This process is part and parcel of the diabetes itself and often so characteristic as to enable the ophthalmoscopic

sions in diabetes, specific

. Combinations of two or three of the lesions are not infrequent Henderson *et al.* found specific diabetic retinopathy in 86 per cent of their diabetics who showed advanced glomerulosclerosis at necropsy However, it may also occur in diabetics who do not have post mortem evidence of glomerulosclerosis. It is there-

The Urine.—Proteinuria occurs in all the clinically recognizable cases and may long be the only sign. Often it is slight or intermittent when first detected. In most patients the proteinuria becomes more pronounced and as a rule becomes sufficiently massive to deplete the plasma albumin. The daily urine may contain more than 10 grams of protein.

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pressure is perhaps a factor in the rarity of malignant hypertension.

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Micro-Aneurysms and Hemorrhages.—The first ophthalmoscopic finding in diabetic retinopathy consists of small red dots, obviously containing ... however, under veins). The

... deeper layers of the retina in the vicinity of the ... the small red areas may persist unchanged for weeks or ... or they may become larger, more ... For months the sanguineous areas may be the only ophthalmoscopic change

The red areas just described were long all regarded as *hemorrhages.* However, in 1943 Ballantyne and Loewenstein[31] demonstrated that some of the red points that have been regarded as hemorrhages are actually micro-aneurysms of the retinal capillaries about 50 to 60 microns in diameter Their pr... show globular distentions of the retinal capillaries bordered by a ... strable and pa... in the inner nu... earliest visible manifestation of diabetic retinopathy and this has been confirmed by subsequent experience. The micro-aneurysms may rupture and produce petechial hemorrhages or perhaps be organized and thus form some of the pin-point "exudates" so often seen in the diabetic fundus. By histological examination, Wexler and Branower[32] found micro-aneurysms in each of 14 and Friedenwald[33] in 57 per cent of 76 diabetic patients They were present in every instance of the Kimmelstiel-Wilson syndrome studied by Ashton[34] The pathogenesis of the micro-aneurysms is obscure; Ballantyne has observed swelling and fatty change in the capillary endo-

... that the micro-aneurysms arise from the venous side of the capillary, and they have been observed in non-diabetics with retinal venous stasis. Of especial interest is Ashton's[35] demonstration of micro-aneurysms in the glomerular tufts in the Kimmelstiel-Wilson syndrome. Friedenwald[36] found that the hyaline in the glomerular nodules and in the walls of the retinal micro-aneurysms are tinctorially identical The findings of Ashton and Friedenwald indicate strongly that the retinal and glomerular lesions are manifestations of the same process in the capillaries Observations with the tourniquet test indicate that capillary fragility is increased in almost all patients with diabetic retinopathy (*cf* Wagener[22]). For an excellent survey of retinal micro-aneurysms, the reader is referred to Wagener[37]

Exudates —The initial hemorrhages of diabetic retinopathy are usually joined by "exudates" Or the latter may be seen alone at the start The

... highly refractile. Sometimes there are also soft, cotton-wool patches,

fore not a result of the renal disease. Diabetic retinopathy is also not du to retinal arteriosclerosis or to hypertension, for it not uncommonly occur in the absence of either or both; Ballantyne[21] found that over 50 per cen of diabetics with retinal lesions have normal blood pressure, though ir my experience hypertension is absent in less than one quarter of patient with diabetic retinopathy. Nor does the incidence of retinopathy hav any relation to the severity of the disturbance in carbohydrate metabolism for it most often occurs in mild diabetics without acidosis and seems to be neither prevented nor improved by insulin control (*cf.* Dolger[11]). At present, little more can be said about the pathogenesis of diabetic retinopathy than that it is an intrinsic manifestation of diabetes. Indeed, it

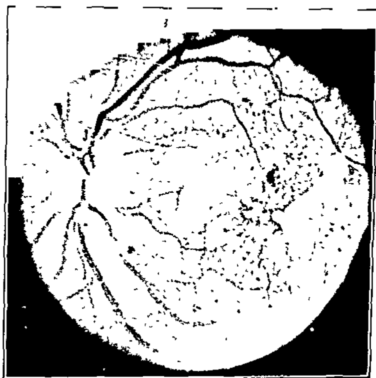


FIG 20 —Retinopathy in diabetic glomerulosclerosis
(Courtesy of the late Dr Robert K Lambert)

appears to be an almost inevitable expression of the disease if the latter lasts long enough, as mentioned above, Dolger observed retinal hemorrhages (probably largely micro-aneurysms) in every one of 200 diabetics followed up to twenty-five years.

What is here termed diabetic retinopathy was long ago described by Hirschberg[22] as pathognomonic of diabetes under the designation "central punctate retinitis." The ophthalmoscopic picture is compounded of microaneurysms, hemorrhages, exudates and changes in the veins. The arteries appear normal unless there is complication by hypertensive or arteriosclerotic retinopathy. Papilledema is not part of the picture of diabetic retinopathy; when present, it results from hypertension.

Of Dolger's
200 diabetics followed up to twenty-five years, ... partially or
totally blind.

TREATMENT

The treatment
available measu
retards their pro
should be adequ...
has not been proved that such control retards the progress of the glomerulosclerosis. As with arteriosclerosis, there are differences of opinion whether or not a well controlled diabetic is less apt to develop glomerulosclerosis than one who is not as careful and goes through repeated acidotic episodes. Brief data from the Joslin Clinic indicating that good control militates against the development of arteriosclerosis and glomerulosclerosis have been published by Mann[29] *et al.* Detailed statistics from the same Clinic collated by Wilson *et al.*[30] indicate that even after twenty to thirty-four years of diabetes patients who have had what they regard as good or excellent control very rarely develop diabetic retinopathy or nephropathy. Likewise, O'Brien and Allen[26] mention briefly that diabetic retinopathy may recede under good control. Contrariwise, Tolstoi[27] and Dolger[18] have not found this to be the case. My observations do not establish that rigid control of the abnormality in carbohydrate metabolism tends to prevent or ameliorate glomerulosclerosis. Many patients who tend to their diabetes with religious fervor develop arterial and renal manifestations. And the fact that in some patients with glomerulosclerosis the disturbance in the carbohydrate economy is so mild that it can be demonstrated only by a glucose tolerance test hardly indicates that meticulous control will avert the glomerular changes. For these reasons, I do not believe it wise to circumscribe the mild diabetic's life too narrowly, and subject him to episodes of hypoglycemia in the hope of averting arteriosclerosis and glomerulosclerosis.

In the vascular manifestations of diabetes, as in arteriosclerosis in nondiabetics, cholesterol restriction and the administration of such lipotropic substances as choline, methionine and inositol have been widely used. However, Keys has shown that cholesterol restriction lowers the cholesterol content of the plasma only if the *total lipid* content of the diet is reduced to

these generally bespeak coincident hypertensive retinopathy, but Wagener finds that they may also result from such complications as pregnancy, carbuncle or gangrene. Wagener states that "the ophthalmoscopically observed white plaques have been shown to consist exclusively of an albumin-rich extravasation into the internuclear layer of the retina with essentially no fibrin masses or cellular elements. Only an occasional fat granular cell is found." Most of these patients have a high beta-globulin content of the plasma and the deposit may well contain giant lipoglobulin molecules.

The Veins.—Nettleship[24] long ago observed dilatation and beading of the retinal veins in diabetes. But only in recent years has there been adequate appreciation of the importance in diabetic retinopathy of changes in the retinal veins and the lesions in the retina and vitreous resulting from the latter. Ballantyne found the retinal veins enlarged and tortuous in about one-third of diabetics and quotes Loewenstein's observation that such dilatation was present in 6 of 15 diabetic children without other ophthalmoscopic changes. Usually later in the course of diabetic retinopathy, the changes in the veins may become severe and have drastic consequences for the eye. The veins may become dilated, beaded and tortuous to such a degree that they have a corkscrew-like course or form loops and varicosities. Networks of what seem to be newly formed veins may appear. These may extend into the vitreous. Histologically, marked phlebosclerosis is found. Venous bleeding leads to large hemorrhages into the retina and/or the vitreous; retinitis proliferans, retinal detachment and secondary glaucoma are among the complications of the late stages. The resulting loss of vision is perhaps the greatest of the tragedies of diabetes, and seems to be steadily becoming more common as diabetics live longer (for discussions of the venous changes *cf.* O'Brien and Allen,[25] Ballantyne, and Wagener).

As indicated above, diabetic retinopathy may be complicated by changes due to hypertension or to retinal arteriosclerosis These hypertensive and arteriosclerotic changes do not differ from those found in nondiabetics and have been described in Chapter 12. The hypertension rarely enters the malignant phase with papilledema.

Arteriosclerotic and Neuropathic Complications.—These are even more common in individuals with glomerulosclerosis than in the general run of diabetics Arteriosclerotic heart disease is the most common cause of death. Arteriosclerotic complications in the extremities and brain are also frequent. Cord bladder and other manifestations of diabetic neuropathy are not rare.

PROGNOSIS

The prognosis of diabetic glomerulosclerosis is poor. Most often the course is downhill, albeit intermittently and not rarely at a slow pace. The average duration of life after the appearance of proteinuria, retinopathy or another initial manifestation is probably about three years. However, some patients get along for six years or even more. Of 22 cases of glomerulosclerosis studied by Rifkin *et al.* at necropsy, 9 succumbed to uremia, 7 to heart failure, 2 to acute coronary occlusion and the others to unrelated causes. Of the 61 necropsy observations of Henderson[7] and his

Chapter

18

THE AMYLOID KIDNEY

cytosis of protein and lipid from the glomerular [illegible]
clinical manifestation is proteinuria, which may be massive enough to entail hypoproteinemia and a nephrotic syndrome. The secondary im- [illegible]

kidney. From the morphological point of view the amyloid kidney is a nephrosis, for the lesions are degenerative, and Volhard and Fahr[1] designated it as amyloid nephrosis. Both the clinical and anatomical pictures of [illegible]

"bacon kidney" [illegible]
is still used by [illegible]
sulphuric acid were described by Meckel,[3] who thought amyloid to be cholesterol. Because of the iodine reaction, Virchow[4] considered the substance to be related to cellulose and, therefore, coined the word amyloid. The term amyloid has persisted, though it is known since the researches of Friedreich and Kekulé,[5] that the substance in question is not a carbohydrate but a protein. The clinical features of amyloid disease of the kidneys were described by Wilks,[6] Todd[7] and Traube.[8]

OCCURRENCE OF RENAL AMYLOIDOSIS

Three etiological categories of amyloidosis may be differentiated:

1. *Primary amyloidosis*, in which the lardaceous deposits develop in the absence of known cause. Long ago described by Litten,[9] such cases are rare, in 1946, Eisen[10] found only 46 in the literature and added 2. In many of these cases the amyloid does not stain classically with Lugol's solution, Congo red and methyl violet (para-amyloid). The distribution of

fats must be excluded. This entails a very rigorous regime, and its value in the treatment of arteriosclerosis and glomerulosclerosis is still decidedly *sub judice*. As has been said, one should beware of merely making the patient's life seem longer without actually prolonging it.

The treatment of edema, renal insufficiency and the other manifestations of ... r from that in ... . Coronary ins ... are treated as in nondiabetics. Perhaps the saddest chapter in the treatment of diabetes is our inability to help diabetic retinopathy. Since the process is characterized by hemorrhages in the early stages, and because increased capillary fragility has been found, rutin and ascorbic acid have been used. In the writer's experience they have been worthless.

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Because
disease, it
following

Age	Number of cases
0 to 10	3
11 to 20	11
21 to 30	21
31 to 40	10
41 to 50	10
51 to 60	3
61 to 70	3
Over 70	0

Of these 61 cases, 36 were in males and 25 in females.

Amyloid disease of the kidneys of any considerable extent is almost always ac ... deposits in the liver and spleen. The adrenals, ...

trachea and larynx

NATURE OF RENAL AMYLOIDOSIS

... tissue ... being ... es and ...

... trogen, yields amino-acids on acid hydrolysis, and is split by proteolytic ferments, though with difficulty It is, therefore, undoubtedly a protein. Krawkow ... sul- ... ind ... is ... ging ... by variations in the staining reactions

The most important color reaction of amyloid is with iodine; Lugol's solution stains it a mahogany or walnut-brown This is sharper after preliminary treatment with acetic acid. Subsequent addition of dilute sulphuric acid may change this to a blue or green tint. With methyl violet and some other dyes, amyloid stains metachromatically, a red color resulting The great affinity of amyloid for Congo red is the basis of a diagnostic test (p 525) These reactions are not invariable; I once saw severe generalized amyloidosis in a syphilitic patient which stained with ... similar case. ... myloid. The ... in primary ... amyloidosis secondary to myelomatosis. These findings indicate that amyloid varies in chemical composition.

... to deposits in the heart, tongue and gastro-intestinal tract. Congestive heart failure, macroglossia and skin lesions are present in considerable proportions of the cases (*cf.* Eisen).

2. *Amyloidosis complicating multiple myeloma.* This occurs in about 5 to 10 per cent of patients with myelomatosis. In these cases the amyloid ... tribution and staining re-...

... *Secondary amyloidosis,* which results from chronic suppuration or certain other processes in which there is great tissue destruction. This is the common variety of amyloidosis; the incidence of the other two types is trivial in comparison.

According to the figures collated by Eisen, the kidney is involved in 26 per cent of cases of primary amyloid, 29 per cent of amyloid complicating multiple myeloma and 72 per cent of secondary amyloidosis. Dahlin[11] found the kidney infiltrated in 93 per cent of his cases of secondary amyloidosis.

Secondary amyloidosis occurs almost exclusively in the chronic cachexias, more particularly those characterized by long-standing suppuration. The most common cause is tuberculosis (41 of Saleeby's[12] 50 cases), especially in the presence of pulmonary cavities or bone or joint sinuses. Amyloidosis is more apt to complicate tuberculosis in an inactive, afebrile stage than when it is progressive and accompanied by high fever. Another common cause in pre-penicillin days was chronic pyogenic infection with long-standing suppuration, as in empyema, osteomyelitis, pulmonary abscess, bronchiectasis, pyonephrosis, etc. Extreme amyloidosis occurred in an instance of long-standing purulent paranasal sinusitis. While amyloidosis due to syphilis is, perhaps, most often found when there are old bone sinuses, yet it may occur, both in the congenital and acquired forms, in the absence of suppuration. In Hodgkin's disease, malaria, leukemia, gout, rheumatoid arthritis and many other conditions, amyloidosis has been described without any suppuration. Breaking-down neoplasms are a rare ... amyloidosis in ulcerative ... en it. Oppenheimer and ... is and multiple gangrene ... the gangrene cleared up. I saw one instance of extreme generalized amyloidosis accompanying subacute bacterial endocarditis, in which it is apparently very rare. Beatty[14] observed 4 cases in which amyloidosis was associated with rheumatic heart disease. I have not seen this association. Since the introduction of the antibiotics, the other improvements in the treatment of tuberculosis and the virtual disappearance of tertiary syphilis, secondary amyloidosis, formerly so common, has decreased enormously in incidence

While amyloidosis is usually found as a result of a long-standing suppuration or other process, yet it can be produced very rapidly. Krawkow[15] found amyloid after eleven days of experimentally produced suppuration in the rabbit. Dickinson[16] saw lardaceous disease three weeks after a compound fracture and other observations of even shorter periods have been reported.

smooth, pale, often glassy, butter-yellow or ochre surface; the French compare the color to that of old ivory. Much less commonly, the kidney is ... brown (red amyloid kidney). The consistency is increased and the ... If there has been very extensive

be greasy ...

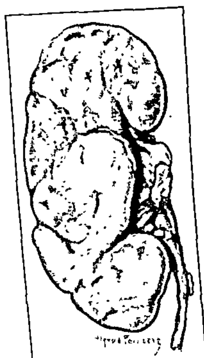


FIG 21 —Amyloid contracted kidney complicating long-standing chronic pneumonitis.

as grayish, translucent dots which may be slightly elevated. Application of Lugol's solution after preliminary treatment with dilute acetic acid produces a brownish stain in which the glomeruli can be seen as dark-brown

reaction is very inconstant. It was mentioned above that even the iodine reaction may be absent despite extensive amyloidosis. Thrombi are sometimes present in the small veins

In the later stages, atrophy of the parenchyma and replacement fibrosis result in the *amyloid contracted kidney*. The kidney becomes smaller and

Amyloidosis can be produced in mice and other animals by causing long-standing suppuration or by the repeated injection of toxins. This was first done by Birch-Hirschfeld[20] in 1882, who produced suppuration in a rabbit by the inoculation of pus from a patient with caries, and observed the development of amyloid in the spleen within six weeks. Since then, amyloid has been produced with pure cultures of staphylococci, Bacillus pyocyaneus and various other organisms, as well as with pyocyaneus and other toxins. Horses used to make diphtheria antitoxin often have amyloid. Frank[21] produced amyloidosis in white mice by the injection of a bacillus of the Friedlaander group, but his conclusion that amyloidosis is always due to such infection is unsupported.

A new line of investigation was opened by the experiments of Kuczynski,[22] who produced amyloidosis in white mice by feeding them with eggs, milk and cheese. He found that while the first degradation products of casein also produce amyloid, peptones do not. From these experiments, Kuczynski concluded that an essential factor in the production of amyloidosis is the circulation of protein complexes that undergo further degradation. In good accord with this view is the fact that amyloid is itself a protein and that it almost always appears in the presence of marked tissue destruction. Letterer[23] and others have brought forward considerable evidence that at least often the proteins in question are globulins and that hyperglobulinemia is often concerned in the genesis of amyloidosis. This view is strongly supported by the experiments of Eklund and Reinmann,[24] who found hyperglobulinemia in rabbits in which amyloidosis was produced by repeated injections of sodium caseinate. Also concordant are the observations of Hoffman[25] *et al.*, who found that protracted feeding of large amounts of cholesterol to rabbits produces hyperglobulinemia and, in some of the animals, amyloidosis. The occurrence of amyloidosis in chronic suppurations, multiple myeloma and antitoxin [illegible] have produced protracted hyperglobulinemia in rabbits by the intravenous injection of rabbit globulin. Some of Dick and Leiter's animals developed amyloid, but others did not. It thus seems that either other factors in addition to hyperglobulinemia participate in the deposition of amyloid or that the latter results from the circulation of only certain, as yet undefined, globulins.

PATHOLOGICAL ANATOMY OF RENAL AMYLOIDOSIS

Small deposits of amyloid may be present in the kidney without any change in the gross appearance of the organ. They may be brought out by the iodine test or discovered only in the sections.

The typical amyloid kidney is enlarged and heavy. While the increase in weight is usually but moderate, it may be very marked; thus, the amyloid kidneys of a girl, aged fourteen years, with tuberculosis of the hip of many years' duration, weighed together 800 grams. The amyloid kidney is generally heavy for its size. There are unusual amyloid kidneys which are smaller than normal. The capsule strips readily, revealing a

retained while the rest of the tı
point to which Fahr[29] has called
to the presence of the amyloid,
the cells of the tuft or capsule is seen. Bell found that there is usually a definite increase in the endothelial nuclei of the glomeruli preceding the deposit of amyloid, which he attributes to the underlying infection. If the process lasts long enough, the final result is complete fibrosis of the glomerulus, connective tissue growing in from the capsule. The next most common seat of amyloid deposition is in the vasa afferentia; the larger arteries are not involved as regularly or as early. The efferent arterioles may be involved in advanced cases, but not as much as the afferent. There are rare cases in which the arteries in the medulla alone are involved.
... between the cells of the media or under the

homogeneous tube. However, Oliver's dissections show ... tion of the amyloid along the arteries is always patchy. Another, less common, site of amyloid change is in the basement membrane of the t... particularly in the medulla. Rare instances have been described

glomeruli, the tubules may be practically normal. But in the large majority of instances, alterations of greater or less extent are found in the tubular epithelium These are usually most marked in the proximal convoluted tubules, and consist in fatty and lipoidal change, appearance of hyaline

lumens simulating casts in the sections are albuminous urine coagulated by the histological fixative and not intra vitam casts. This is probably true of most of the structures in the proximal parts of the nephron. Some of the actual casts in the lower nephron plug the lumen with upstream dilatation and doubtless ultimate atrophy. Saleeby[12] found that the casts do not give the amyloid staining reactions However, on rare occasions the amyloid basement membrane may fuse with the epithelial cells and the cast-off mass give the amyloid staining reactions (Senator[31]). It may have been such masses that were described and figured by Dickinson[32] and other older authors as amyloid casts in the renal tubules. Recently, Iverson and Morris[33] have demonstrated tinctorially the presence of amyloid casts in the rare primary amyloidosis.

In older cases, extensive atrophic changes in the tubules take place. At first, these consist in atrophy and collapse of individual tubules with

harder, the capsule adherent and the surface irregularly granular. In some cases, despite well-marked contraction, there is little irregularity of the surface. The grayish-yellow section shows narrowing of the cortex, obliteration of the markings and absence of sharp transition between the cortex and medulla. The presence of amyloid in such a kidney can sometimes be recognized only by the application of iodine or microscopically. Grossly, the kidney may be indistinguishable from that of chronic glomerulonephritis. The amyloid contracted kidney does not attain the extreme degree of shrinkage that is sometimes seen in the primary or secondary contracted kidney.

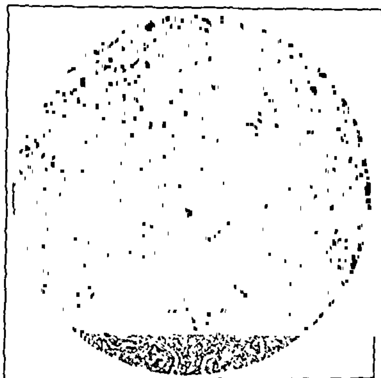


FIG Most of the glomeruli have nsive atrophy and dis- appeai

Microscopically, it is seen that the amyloid is deposited almost entirely in the walls of the vessels, thereby accounting for the difficulty of injecting amyloid kidneys which Virchow long ago noted The glomeruli are almost always involved, and sometimes are the exclusive site of the deposition. Amyloidosis results in great enlargement of the glomeruli, though they may ultimately shrink. The amyloid is laid down in the capillary loops around the endothelium. With the azocarmine stain, Bell[23] has demonstrated that the amyloid is deposited on the inner surface of the basement membrane, often displacing the endothelial nuclei inwards. The final result of the process is the conversion of the tuft into an amyloid sphere in which are to be seen only remains of nuclei, and sometimes not even these. But it is surprising how long the permeability of individual capillary loops may be

in the kidneys. On the other hand, in still other cases, renal amyloidosis does produce important symptoms. There are edema and, in unusual cases of amyloid contracted kidney, renal insufficiency, with yet more

hypertension . . . Most commonly, it is

. . . of about 2000 cc.

daily

patient with amyloid kidney wi

If edema is forming or the patien

there may be oliguria with dee

urine with low specific gravity is encountered . . . The onset of

of amy

The

great

urine daily

practically disappear Cases have been described in which well-marked amyloidosis of the kidneys was not accompanied by any proteinuria whatsoever, despite careful observation of the urine for a long period before death (Leube[37]) It was mentioned on page 121 that the albumin to globulin ratio in the urine in amyloid nephrosis is very low. The number

of casts present

uria in other fo

The casts are

also present

the latter are not characteristic of amyloid disease was emphasized above. Fatty and not uncommonly lipoidal (double refracting) casts may be found. As a rule, cellular elements are sparse, but occasionally moderate numbers of red cells are present.

The Blood —It need scarcely be mentioned that anemia is often present as a result of the primary disease. If much protein is lost in the urine, the total protein content of the plasma is lowered There may even be less than 4 per cent of plasma protein This has several times seemed to me to

liver interfere with regeneration, in fact, plasma protein concentrations well below the normal are not uncommon in cachectic tuberculous patients without any amyloidosis or other cause for loss of protein in the urine. The albumin to globulin ratio is usually inverted in such cases, sometimes markedly so Here, again, the basic disease is unquestionably partly at fault, for a rise in globulin is common in tuberculous and other infections. Sometimes the lowered protein content of the plasma is accompanied by hypercholesteremia, as in other patients who lose protein in the urine. I have several times seen the blood cholesterol well above 300 gm. per cent, and in one patient who was not cachectic it exceeded 600 mg. per cent. The cachectic state of most of the patients is probably the reason

small areas of replacement fibrosis. In the fully developed amyloid contracted kidney, the field consists largely of cellular connective tissue in which are mostly amyloid and fibrotic glomeruli and atrophic tubules. There are often also islands of greatly dilated tubules lined by low epithelium, the entire picture closely resembling that seen in other varieties of contracted kidney. Only in long-standing amyloidosis, among the nephroses, did Oliver's studies reveal disorganization of the architecture of the kidney. In such cases the vessels may show well-marked endarteritis and arteriosclerotic change, but Oliver found that this occurs only in older individuals.

The interrelations of the amyloid transformation of the glomeruli and the degenerative changes in the tubules are of interest. It is to be remembered that amyloidosis almost always occurs in toxic states in which tubular degeneration is common even when amyloidosis is absent. In their first monograph, Volhard and Fahr[1] considered the amyloid change and the tubular lesions as independent consequences of the general toxic state, viewing the actual amyloid change as relatively unimportant in the causation of the symptoms and as merely an unessential "complication" of the nephrosis manifested by the tubular lesions. Later, Fahr[34] regarded the atrophic changes in the tubules as secondary to the glomerular amyloidosis, but the hyaline-droplet change in the tubules as independent. In view of the fact that almost the entire blood supply of the tubules first passes through the glomeruli, it would seem that so great an interference with the glomerular circulation as is undoubtedly caused by the amyloid change in the glomerulus must result in atrophic and degenerative processes in the appertaining tubule. Moreover, the degenerative changes in the kidneys of tuberculous patients without amyloidosis are, at least as far as I have observed, but rarely even nearly so marked as one commonly sees with amyloidosis. The view that the atrophic changes in the tubules with the formation of the amyloid contracted kidney are secondary to the glomerular changes seems to me undoubtedly correct, for nephrotic contracted kidneys in the tuberculous without amyloidosis are extremely rare; in rather large material, I have never encountered one. Moreover, lipid and hyaline droplets in the tubular epithelia may well be due to athrocytosis of lipid
and pro[illegible]
heighten [illegible]
toxemia [illegible]
seem tha [illegible]
lesion of [illegible]
of some of the nephrons.

CLINICAL PICTURE OF RENAL AMYLOIDOSIS

In most instances, amyloid disease of the kidneys is of little clinical importance, the picture being entirely dominated by the basic illness. A number of cases have been recorded in which the urine was free from pathological constituents and yet well-marked amyloid change in the kidneys was found postmortem. Most often, there are urinary changes, but the clinical course of the patient is not influenced by the presence of amyloid

Wagner, ...
patient with am
author,[39] the blood pressure ... and had been considerably higher prior to admission to the hospital. I have since seen several other instances of hypertension due to amyloid contracted kidney. It is, of course, obvious that the cachectic condition of most of these patients tends to inhibit the maintenance of hypertension and the development of cardiac hypertrophy, even if the essential factors for their production are present. It is perhaps for this reason that hypertension is rarest in the cases due to pulmonary tuberculosis.

Hypertensive Retinopathy.—Hypertensive retinopathy is extremely rare, as one would expect from the rarity of hypertension. Litten[40] saw it but ... cases of amyloid disease, and Dickinson[41] and

Diarrhea.—Diarrhea may be present as an evidence of ... lyoidosis.

DIAGNOSIS OF AMYLOID KIDNEY

If, in the presence of chronic tuberculosis or a long-standing suppuration, the liver and spleen ... them to be amyloid, ... kidneys is also present. ... and there are few or no casts in the urine. In the absence of demonstrable amyloidosis of the liver and spleen, the diagnosis of amyloid nephrosis is much more difficult The urinary findings detailed above and edema in the absence of hypertension and nitrogen retention may, of course, occur in chronic nephrosis without amyloid Glomerulonephritis in a cachectic patient may have the same clinical features Nevertheless, if such a nephrotic picture—marked proteinuria and edema with neither impairment ... e presence of chronic ..., it is highly probable ... ferentiation of amyloid nephrosis and the cachectic edema that is so common in the terminal stages of pulmonary tuberculosis is often difficult, for the latter may be accompanied by febrile proteinuria The same is true, unless enlargement of the liver and spleen is present, of the diagnosis of amyloid contracted kidney with renal insufficiency and perhaps hypertension from chronic glomerulonephritis in patients with chronic suppurations.

The Congo Red Test.—Bennhold[42] introduced a test for amyloidosis based on the great affinity of the colloidal dye Congo red for amyloid. He found that if 10 cc. ... venously, less than ... normal persons with ... in the presence of amyloid disease, from 40 to 100 per cent leaves the blood stream within an hour. Bennhold also found that in chronic nephrosis,

why the cholesterol of the blood is not as much elevated as in other varieties of renal disease with low plasma protein. I have twice seen lactescent serum in such patients. Nitrogen retention occurs in the rather unusual cases with renal insufficiency and may reach extreme degrees.

Edema.—Edema is a very common and sometimes outstanding symptom of amyloid nephrosis. Dickinson found subcutaneous edema in 33 of 48 patients with amyloid kidney. It is usually of insidious onset. As a rule, the lower extremities are first and most affected, but the face may be puffy and in unusual instances great general anasarca develops. Ascites is not uncommon, having been present in 12 of Dickinson's cases. This author found hydrothorax in but one of the patients. There may be ascites in the absence of anasarca. I have examined the subcutaneous edema fluid on a number of occasions, and found that it is of the type that occurs in nephrotic edema; *i. e.*, it is very poor in protein. On all occasions the protein content was under 0.5 per c[illegible] there was almost no protein. [illegible] fluid, and in one of these cases that came to necropsy was able to prove that this was not due to local disease of the peritoneum. Both patients had hypercholesteremia, and in one the serum was also lactescent. The edema is, therefore, of the nephrotic type, due to the diminished albumin content of the blood plasma.

It should be borne in mind that in patients in the final stages of tuberculous and other cachexias, edema, particularly of the lower extremities, is common even in the absence of amyloid disease—so-called cachectic edema. In such cases there may be low plasma proteins with inversion of the albumin to globulin ratio and low protein content of the edema fluid. It, therefore, seems probable that an important factor in the genesis of cachectic edema is diminished colloid osmotic pressure of the plasma, though in such patients cardiac weakness doubtless also plays a part In cachexias with amyloidosis, the loss of protein in the urine is, accordingly not the only factor which lowers the blood protein and thus leads to edema. But edema is seen also in some patients with amyloid nephrosis who at the time are not at all cachectic, the loss of protein in the urine being the only discernible factor in the pathogenesis of the dropsy. In the rare primary amyloidosis, edema is most often part of the picture of congestive heart failure.

Renal Insufficiency.—Renal insufficiency with consequent nitrogen retention and uremia occurs in unusual instances of the amyloid contracted kidney. It is possible that such cases are not so rare as is generally thought; because of the desolate general condition of the patient, the blood chemistry is usually not adequately studied. However, it is often striking how extensive may be the amyloid change in the kidneys without producing renal insufficiency. Almost all the glomeruli seen in the sections may be converted to amyloid and yet the patient at no time gave any evidence of uremia. This may be explained by the fact, mentioned above, that isolated capillary loops often remain permeable in an otherwise completely amyloid glomerulus. The patient may remain for a long time in a state of compensated impairment of renal function, as shown by diminished ability to concentrate the urine but absence of retention in the blood.

Wagner, ...
patient with amyloid contracted kidney ... author,[39] the blood pressure was 196 mm. systolic and 116 mm. diastolic, ... considerably higher prior to admission to the hospital. I ... hypertension due to amyloid ...

Hypertensive ... as one would expect from the rarity of hypertension ... twice in several hundred cases of amyloid disease, and Dickinson[41] and Noble and Major[42] each mention an example. Arteriosclerotic retinopathy was present in the patient referred to in the preceding paragraph.

Diarrhea.—Diarrhea may be present as an evidence of intestinal amyloidosis

DIAGNOSIS OF AMYLOID KIDNEY

If, in the presence of chronic tuberculosis or a long-standing suppuration, the liver and spleen are enlarged, smooth and hard, so that we believe them to be amyloid, it is extremely probable that amyloid disease of the kidneys is also present This holds true even though proteinuria is slight, and there are few or no casts in the urine In the absence of demonstrable amyloidosis of the liver and spleen, the diagnosis of amyloid nephrosis is much more difficult The urinary findings detailed above and edema in the absence of hypertension and nitrogen retention may, of course, occur in chronic nephrosis without amyloid Glomerulonephritis in a cachectic patient may have the same clinical features Nevertheless, if such a nephrotic picture—marked proteinuria and edema with neither impairment ... presence of chronic ... highly probable ... differentiation of amyloid nephrosis and the cachectic edema that is so common in the terminal stages of pulmonary tuberculosis is often difficult, for the latter may be accompanied by febrile proteinuria The same is true, unless enlargement of the liver and spleen is present, of the diagnosis of amyloid contracted kidney with renal insufficiency and perhaps hypertension from chronic ...

... based on the great affinity of the Congo red ... found that if 10 cc of a 1 per cent solution of Congo red is injected intravenously, less than 30 per cent of it disappears from the blood stream of normal persons within an hour On the other hand, Bennhold stated that in the presence of amyloid disease, from 40 to 100 per cent leaves the blood stream within an hour. Bennhold also found that in chronic nephrosis,

the dye likewise leaves the blood stream more rapidly than normally, values of 40 to 60 per cent being found, but not over 60 per cent as in amyloid. Bennhold believed the rapid disappearance of the dye from the blood in amyloidosis to be due to two factors: (1) The dye is adsorbed by amyloid, as he showed experimentally; (2) lowered adsorption by plasma albumin, the concentration of which is diminished in these conditions. It seems probable that increased permeability of the kidney also plays a part in the rapid disappearance of the dye from the blood stream when there is marked proteinuria, the dye leaking into the urine.

Bennhold's findings were confirmed by Bookman and Rosenthal[44] and others, and the Congo red test has since been widely used for the detection of amyloidosis. However, shortcomings soon became evident. While Lipstein[45] found that more than 90 per cent of the Congo red was absorbed in 29 of 34 tuberculous patients with amyloidosis verified at necropsy, he also observed absorption of between 80 and 100 per cent of the dye in 4 of 91 individuals without tuberculosis. Selikoff[46] has studied the test in great detail and finds that the original criteria lead to both false negatives and positives. Up to 90 per cent absorption may be found in chronic nephrosis and in other conditions without amyloidosis On the other hand, patients with small amounts of amyloid often have less than 90 per cent absorption. Less than 90 per cent absorption thus does not speak strongly for or against the diagnosis of amyloidosis. More than 90 per cent removal favors the diagnosis of amyloidosis, but exceptional instances of even 100 per cent absorption in the absence of amyloid have been observed. Selikoff states that he has not seen any case in which practically complete absorption of the dye occurred in 2 consecutive Congo red tests in the absence of amyloid. Unger[47] *et al.* have modified the technique of the Congo red test in several ways, including a thirty-minute end point, and find that the accuracy in testing for amyloid is improved. Severe reactions have occurred from some batches of Congo red (Selikoff and Bernstein[48]).

It was mentioned above that histologically the deposits in primary amyloidosis do not usually stain well with Congo red, and correspondingly Eisen[10] states that the Congo red test is more often negative than positive in this rare form of amyloidosis

Biopsy —The diagnosis of amyloidosis can often be established by aspiration biopsy of the liver or spleen (*cf* Waldenstroem[49]) Selikoff and Robitzek[50] have introduced gingival biopsy for this purpose In 18 patients with a clinical diagnosis of amyloidosis, they obtained 14 positive biopsies, including cases with negative Congo red tests.

PROGNOSIS OF RENAL AMYLOIDOSIS

The prognosis in the vast majority of cases is that of the basic disease, which usually leads to death within a year or less. But cases are not rare in which amyloidosis, due to such cases as tuberculosis of the bones or syphilis, lasts for years. One of Wagner's[18] patients had amyloidosis for fifteen years.

with suppuration in an extremity which can be cured by antibiotics or amputated, and to instances of pulmonary tuberculosis or empyema which heal spontaneously or are cured by medication or operation. A number of cures thus attained have been reported (Gairdner,[51] Herringham,[52] Waldenstroem,[49] Reinmann,[53] and others). That amyloid can be completely absorbed once the cause has been removed is known from the experiments of Kuczynski,[22] who produced amyloid by feeding casein to mice and saw it disappear after the feeding had been stopped. In amyloidosis induced in rabbits by bacterial injections, Dick and Leiter[26] observed reabsorption of amyloid after discontinuing the injections, but not in the kidneys.

TREATMENT OF RENAL AMYLOIDOSIS

The treatment of the patient with renal amyloidosis comprises (1) the therapy of the underlying disease (tuberculosis, osteomyelitis, syphilis, etc.), and (2) the management of such manifestations of the renal implication as hypoproteinemia, edema, renal insufficiency, hypertension and heart failure, much as in other forms of renal disease. It is to be borne in mind that amyloidosis may disappear if the underlying cause is eliminated. If syphilis is the basis, vigorous antiluetic treatment is to be pursued. Evidences of early amyloidosis in a tuberculous patient call for especially vigorous treatment with streptomycin and the newer chemotherapeutic

all the symptoms of amyloid kidney, amyloid liver, albuminuria and every possible symptoms of a constitution infected with amyloid disease. He had been considered in the first instance too ill to be operated upon. But nevertheless, a venturesome surgeon did it He took off his leg. This patient had reached the last degree of exhaustion connected with amyloid supervening upon disease of his bones The result of the operation was a perfect return of the normal state"

Fortunately, the once common and usually irremediable problem of amyloidosis is a vanishing one The elimination of gummatous luetic disease, the decline in the incidence of tuberculosis and the control of pyogenic infections by antibiotics have almost eliminated clinically significant amyloidosis

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Chapter

19

ACUTE . ETIOLOGY, BACTE ANATOMY

Acute glomerulonephritis is a diffuse inflammation of the glomeruli of ... lesions however, are indicated by some evi-

It would be more accurate to use the term acute diffuse glomerulo-

point of view than the focal affections. In the past few years, the term glomerular nephritis is being used with increasing frequency instead of glomerulonephritis

The conception that one form of Bright's disease starts as an inflammation of the glomeruli, a glomerulonephritis, was introduced by Klebs[1] as a result of his observations on postscarlatinal renal disease and definitely established seventy-five years ago by the histological investigations of Langhans[2] Numerous studies during World War I showed that trench nephritis is an acute diffuse glomerulonephritis The investigations of Loehlein,[3] confirmed in this country by Bell and Hartzell,[4] have demonstrated clearly that the highly variegated clinical and anatomical pictures of chronic glomerulonephritis are later stages of acute glomerulonephritis, the tubular, interstitial and vascular changes all ensuing subsequent to the stage of acute glomerulitis which forms the subject matter of this chapter

ETIOLOGY OF ACUTE GLOMERULONEPHRITIS

Acute glomerulonephritis is a manifestation of an infection in one part or another of the body While cold and other factors often play an important part as predisposing causes, recent investigations have shown more and more clearly that the primary and essential cause is infection. Longcope[5] and his coworkers were able to demonstrate infectious foci in

85 per cent of their cases of acute glomerulonephritis. The relation between the initial infection (sore throat, scarlet fever, etc.) and the renal lesion is generally clear in children, but in adults there is a larger proportion of cases in which a history or other evidence of a preceding infection cannot be obtained. In fact, in 2 of the above-mentioned cases studied by Longcope, the infectious focus could not be demonstrated even at necropsy. Nevertheless, these "idiopathic" cases are in all ways so nearly identical with those occurring in connection with a manifest infectious focus, that their origin in infection seems beyond cavil.

In 976 cases of acute glomerulonephritis, including 77 of their own, Hayman and Martin[6] found the following preceding infections:

Antecedent infection	*Number of cases*
Sore throat, tonsillitis	313
Upper respiratory tract	238
Otitis and sinusitis	56
Scarlet fever	62
Skin infections	40
Pneumonia	39
Rheumatic fever	17
Miscellaneous	101
Infection unknown	110

Occurrence.—Infection in the lymphoid tissue of the throat preceded about 90 per cent of the unequivocal cases of acute glomerulonephritis in adults seen by the writer, *i. e.*, those patients who had edema, hypertension or renal insufficiency so that focal nephritis could be ruled out with certainty. Indeed, in my experience in New York City in recent years, typical acute glomerulonephritis due to causes other than sore throat has been very exceptional. When acute glomerulonephritis develops in patients with otitis, mastoiditis, sinusitis or bronchitis, and is attributed to the latter, there is most often an antecedent streptococcic infection in the lymphoid tissue of the throat. Those series of cases of acute nephritis in adults in which a high proportion are listed as due to causes other than sore throat probably include considerable numbers of patients with focal nephritis. Many of the older clinicians did not differentiate adequately between diffuse glomerulonephritis and other forms of Bright's disease. This was particularly true of the renal complications of erysipelas, typhoid fever, various forms of sepsis, pneumonia and other infections, which were usually designated as "acute nephritis" or "hemorrhagic nephritis," without any attempt to make the important differentiation between focal nephritis and diffuse glomerulonephritis In New York City, in recent years, the importance of scarlet fever in the etiology of acute glomerulonephritis has become far less than it was previously

Tonsillitis and Other Varieties of Sore Throat.—The foregoing table and discussion emphasize the great importance of demonstrable infections of the lymphoid tissue of the throat, particularly tonsillitis, in the etiology of glomerulonephritis. It is probable, moreover, that a considerable proportion of the cases of unascertained etiology and of those following exposure to cold has been preceded by mild throat infections which did not attract

attention. T ... by infections of the tonsillar ring in the etiology ... recent years, ... tonsillar abscess. As mentioned above, ...

a few days or even a week or two after subsidence ... showing an analogy to the course of events in scarlet fever. Glomerulonephritis may follow very mild attacks of tonsillitis as well as severe ones and peritonsillar abscess. However, Seegal and Earle[7] found that the antecedent infection is more often severe ("deep") in glomerulonephritis than in rheumatic fever. When glomerulonephritis occurs in the presence of chronically diseased tonsils, it is usually difficult to decide whether the latter were concerned in the genesis of the renal condition. Glomerulonephritis may follow tonsillitis which has been treated promptly with a s... ...icillin or another antibiotic. Whether such treatment c...

in 479 cases of angina.* Slight proteinuria at the height of the fever is, of course, much more common, but differs in no wise from "febrile albuminuria" in other pyrexias. Focal nephritis may also occur (Chapter 23).

The close but as yet totally unexplained, relation of tonsillar infection ...

tonsils are removed in a patient with subsiding glomerulonephritis, there is often an exacerbation of the hematuria and less frequently of other symptoms, several authors mention this and I have seen it a number of times. However, the same phenomenon may occur after operations on other infectious foci, and most often there is little immediate change in the urine following tonsillectomy.

Scarlet Fever.—Proteinuria is encountered at the height of the fever in a large proportion of patients with scarlatina, to pass off with defervescence. Focal nephritis also occurs in a small fraction of the cases during the febrile period. Septic cases may be complicated, usually during the first week but sometimes later, by acute interstitial nephritis. But by far the most important of the renal complications of scarlet fever is acute glomerulonephritis. It is often aptly termed postscarlatinal glomerulonephritis, for it occurs almost invariably from the second to the sixth week of the disease, after the symptoms have passed away and desquamation is taking place. It may occur as late as the seventh week. The most common time

of onset is between the eighteenth and twenty-second days. Barasch[10] observed the following dates of onset in 121 cases of postscarlatinal glomerulonephritis:

Day of scarlatina	*No of cases*
5 to 9	1
10 to 14	10
15 to 19	26
20 to 24	44
25 to 29	20
30 to 34	10
35 to 39	7
40 to 45	3

Postscarlatinal glomerulonephritis is thus one of the group of manifestations of scarlet fever that generally appears after the disease is seemingly over. The intimate interrelations of these late affections have been especially studied by Schick[11] and Pospischill[12] and the entire group termed by the latter "the second sickness." The manifestations of the second sickness are lymphadenitis, glomerulonephritis, fever without readily discernible cause, angina, relapse of the scarlet fever, endocarditis, synovitis and erythema (Jochmann[13]). These occur individually or in any combination. The most important of them is glomerulonephritis.

The incidence of postscarlatinal glomerulonephritis apparently varies enormously with the *genius epidemicus*. Some years it is much more than others. McCrae[14] found well-marked urinary changes after the febrile period in 10 per cent of 1034 cases of scarlet fever; about 5 per cent showed sufficiently marked abnormalities to warrant the diagnosis of nephritis, and in about 2 per cent there were extrarenal manifestations of nephritis. Rolly[15] observed postscarlatinal glomerulonephritis in 7 per cent of 1400 cases. Steiner and Johannessen[16] studied an epidemic of scarlet fever in which over 70 per cent of the cases were complicated by nephritis. On the other hand, Caiger[17] found nephritis in only 3.32 per cent of 2078 cases of scarlet fever. Friedländer[18] encountered postscarlatinal glomerulonephritis in 42 of 229 necropsies on scarlet fever patients. Scarlet fever is much less apt to be followed by glomerulonephritis in adults than in children; thus, Caiger found the incidence of nephritis in scarlet fever to be 3 6 per cent in children under fifteen years of age, but only about 0 75 per cent in patients over that age. In recent years the incidence of postscarlatinal glomerulonephritis in New York City has been very low, and this seems to have been true in various parts of the United States. Thus, Lucchesi and Bowman[19] found that nephritis complicated only 1.26 per cent of 5377 cases of scarlet fever.

This great decrease in the incidence of postscarlatinal glomerulonephritis in recent years has been noted in various parts of the world It is not alone, if at all, due to improvements in therapy, for it antedated the introduction of antitoxin, sulfonamides and penicillin. The decline may be correlated in some way with the far lesser severity of scarlet fever in recent decades, but nephritis may follow very mild scarlatina. The possibility exists that the lesser incidence of nephritis may result from a change in the

[illegible] Nevertheless, in some [illegible]

[illegible] the most common cause of [illegible] London Hospital for Sick Children, admitting all varieties of diseases, Dickinson[20] found that 75 of 80 cases of nephritis were due to scarlet fever. [illegible] New York City, at present, the proportion of cases of glomerular [illegible] In fact, in recent years [illegible]

[illegible] while below one year it was but 4 5 per cent. In adults, [illegible] less important as a cause of acute glomerulonephritis, Dickinson finding but 7 of 50 cases due to it [illegible] equally liable, but that am[illegible]

Ly[illegible] found that the [illegible] fever [illegible] now[illegible] sediment count, he found [illegible] increases in the excretion of protein and formed elements in the urine b[illegible] forty-five days after the onset of scarlet fever.

[illegible]

glomerulonephritis in 9 of 77 necropsies on individuals with subacute bacterial endocarditis, from which they conclude that glomerulonephritis complicates this disease in a higher proportion of cases than any other ailment with the possible exception of scarlet fever. Indeed, lesser degrees of cellular proliferation within the glomeruli, not meriting the designation glomerulonephritis, are even more common in subacute bacterial endocarditis, Christian[25] found them in 80 per cent of his cases. Baehr and Lande were, of course, careful to differentiate glomerulonephritis from focal glomerular lesions, which were so common in subacute bacterial endocarditis in pre-penicillin days Of their 9 cases of glomerulonephritis, 2 were acute and 7 chronic Libman[26] observed that "cases which come under observation in the bacteria-free stage present glomerular nephritis at least fifteen times as often as it occurs in the active stage of the disease," an important difference (see page 555) that is borne out by the extensive investigations of Baehr Libman[27] pointed out in his original description that the clinical picture of the bacteria-free stage of subacute bacterial endocarditis is often completely dominated by the manifestations of glomerulonephritis. It will be mentioned below that glomerulonephritis may occur

also in subacute bacterial endocarditis due to influenza bacilli pneumococci or gonococci.

Antibiotics seem almost to have eliminated glomerulonephritis as a manifestation of subacute bacterial endocarditis. Spain and King[28] report that while diffuse glomerulonephritis was found at necropsy in 33 per cent of 52 untreated cases, it was not found in any of 25 treated cases. I have not seen glomerulonephritis in subacute bacterial endocarditis in the past two or three years.

Pneumonia.—Though febrile proteinuria is common in lobar pneumonia, glomerulonephritis is an extremely rare complication. For statistics in the incidence of glomerulonephritis in lobar pneumonia, it is necessary to rely on older observations because of the remarkable therapeutic efficacy of sulfonamides and penicillin in pneumococcic pulmonary infections. Nauwerck encountered acute nephritis in 2.3 per cent of 550 cases of primary lobar pneumonia, Fraenkel and Reiche[29] in 0.6 per cent of 956 cases, and West[30] not once in 100 cases. Judging by the descriptions of the cases, in

which he regards as "pneumococcal lipoid nephrosis," but at least some of which would fall within the concept of glomerular nephritis as used in this book and by most contemporary clinicians. In a careful study of the kidneys in lobar pneumonia, using accurate methods, Goldring[32] encountered only 2 certain instances of glomerulonephritis in 44 adult patients. Seegal[33] observed only 7 cases of glomerular nephritis in 1007 patients with pneumococcic lobar pneumonia. While most of the anatomical findings are likewise those of focal nephritis, Nauwerck and von Kahlden[34] found glomerulonephritis at necropsy. In other cases, only tubular lesions are found. Blackman[35] has produced glomerular lesions by the repeated injection of pneumococcal autolysate, but the identity of the changes with those of human glomerulonephritis is still *sub judice* However, that pneumococci can cause true glomerulonephritis would seem to be demonstrated by a case of subacute bacterial endocarditis due to pneumococcus Type II, observed at Mount Sinai Hospital, in which typical subacute glomerulonephritis was found at necropsy Nauwerck found pneumococci in large numbers in the kidney of a patient who succumbed to glomerulonephritis complicating pneumonia, but this is not significant for they may be present in the absence of renal disease. It need scarcely be added that pneumonia complicates glomerulonephritis far more commonly than the reverse, such complicating pulmonary inflammations are generally bronchopneumonic in type but may be typical lobar pneumonia. I have not seen glomerulonephritis complicating pneumonia since antibiotics came into use

In the rare cases in which glomerulonephritis does complicate pneumonia, it may occur either at the height of the disease or after the crisis. In Seegal's cases, glomerulonephritis generally appeared two or three weeks after the onset of the pneumonia.

Using the urea clearance test, Goldring[32] found excellent renal function to be the rule during the acute stage of the disease. Only 2 of 13 patients studied developed impairment of renal function during the acute stage and

Tuberculosis.—In incipient tuberculous patients with fever, protein may be found in the urine, but this febrile proteinuria seems to be less common than in diseases with high and continuous pyrexia, as typhoid fever and pneumonia. Maurice Fishberg[61] found proteinuria in but 9 of 100 patients with early but active pulmonary tuberculosis. Teissier[62] and other French clinicians describe an *albuminurie pretuberculeuse*, but there is no evidence that proteinuria precedes the onset of tuberculosis ... now. In advanced pulmonary tuberculosis and exten-

...

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It has not been demonstrated whether the glomerulonephritis of tuberculous patients is due to the toxic products of the tubercle bacillus itself,

...

Trench Nephritis (*War Nephritis*).—During World War I, large numbers of cases of acute glomerulonephritis occurred among the men on both sides of the front. A similar high incidence of renal disease was observed in the Civil War from March, 1862 to March, 1863, but not in the Franco-German, Spanish-American, Boer, or Russo-Japanese wars (Langdon Brown[65]). There were few cases during the first year of the war, but in the course of 1915 the incidence of the disease assumed almost epidemic proportions among the Allied troops. On the German side, likewise, the

segmental. A varying proportion of loops in a glomerulus and of glomeruli in a kidney may be involved. Some of the thickened loops become necrotic and others are occluded by what may be either extreme thickening of the wall or hyaline thrombosis. Klemperer and his associates found that necrosis of loops occurs also in the absence of wire loop lesions and is more common than the latter. The appearance designated as the wire loop lesion is not specific for Libman-Sacks disease; Klemperer *et al*, observed it in 5 of 43 cases of subacute and chronic glomerulonephritis, but here it was accompanied by proliferative and exudative changes. Wire loop lesions have been observed in scleroderma but are rare in this

altered; there are often moderate lipid and other regressive changes, and casts may be seen. Fibrinoid degeneration and necrosis of arterioles and arteries may be present, as may periarterial cellular infiltration.

The nature of the glomerular lesions of Libman-Sacks disease and their relation to classical glomerulonephritis are obscure. It is possible, but purely hypothetical, that the thickening of the loops results in some obscure fashion from the hyperglobulinemia, notably gamma hyperglobulinemia (Walker and Benditt[57]), that is present.

The renal lesions of disseminated lupus erythematosus result in proteinuria, cylindruria and hematuria of varying degrees. Pus clumps are common and the cases sometimes pass for pyelitis for a considerable time. Krupp[58] has pointed out that the urinary sediment in disseminated lupus may be remarkably variegated, containing at the same time red blood cells, red cell casts, oval fat bodies, fatty casts, and broad casts. Impairment of renal function with hyposthenuria and azotemia may develop and many of the patients succumb to uremia. Hypoproteinemia and edema are common, and in some of the cases hypercholesteremia completes the nephrotic syndrome. Hypertension is exceptional and rarely more than slight I have not seen hypertensive retinopathy. Sometimes it is the appearance of proteinuria and impairment of renal function in an obscure fever that first leads to the suspicion of Libman-Sacks disease

Erythema Nodosum.—(
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cases and found by Addis
erythema nodosum had an increase in the number of red blood cells in the urine at the height of the eruption. Since erythema nodosum is probably a nonspecific allergic manifestations, and many of the patients have beta-hemolytic streptococci in the throat, the occasional occurrence of glomerular changes is not surprising.

Influenza.—Influenza is complicated by acute glomerulonephritis on rare occasions. That the influenza bacillus itself can cause this renal lesion is shown by Libman's[59] observation, that subacute bacterial endocarditis due to the bacillus of Pfeiffer may be complicated by glomerulonephritis In one of these cases, in which influenza bacilli were cultured from the blood, I observed typical subacute glomerulonephritis. In the unusual cases of the last influenza epidemic in which glomerulonephritis developed, it was not clear to which microorganism the renal complication was attributable. Widal, Lemierre and Vallery-Radot[60] state that the kidney was involved more often in the epidemic of 1889; on both occasions, the renal disease became chronic in some instances.

Tuberculosis.—In incipient tuberculous patients with fever, protein may be found in the urine, but this febrile proteinuria seems *to be less* common than in diseases with high and continuous pyrexia, as typhoid fever and pneumonia. Maurice Fishberg[61] found proteinuria in but 9 of 100 patients with early but active pulmonary tuberculosis. Teissier[62] and other French clinicians describe an *albuminurie prétuberculeuse*, but there is no evidence that proteinuria precedes the onset of tuberculosis with notable frequency. In advanced pulmonary tuberculosis and extensive tubercle
origins It n
kidneys, cardiac insufficiency
ulonephritis or chronic nephrosis.

"Nephritis" has been stated by many authors to be a common complication of pulmonary phthisis, but this is an error due to basing the diagnosis of nephritis on the presence of proteinuria or edema. We have just mentioned the various causes of proteinuria in tuberculous subjects. Likewise, edema in such patients is generally not "nephritic," but much more often results from amyloid disease or cardiac failure, and in terminal cases dropsical swelling is often seen purely as a manifestation of the

True glomerulonephritis is a very rare complication of pulmonary tuberculosis, having been found by Holten[63] in but 15 of 2800 admissions. He observed it in incipient cases as well as advanced. However, I have seen fairly well-marked reactive changes in the glomeruli with greater frequency than this, but there was usually no clear-cut evidence during life of glomerulonephritis. When glomerulonephritis does complicate active pulmonary tuberculosis, it is notable that arterial *hypertension is usually* lacking or slight, presumably because of the hypoplastic cardiovascular apparatus of most tuberculous patients and the general weakness. Edema and uremia occur, but are rare, I have seen hypertensive retinal lesions only twice, both times in patients with fibroid phthisis.

It has not been demonstrated whether the glomerulonephritis of tuberculous patients is due to the toxic products of the tubercle bacillus itself, to secondary invaders in cavities, or is entirely independent of the tuber-

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Erythema Nodosum.—On extremely rare occasions, glomerulonephritis appears in patients with erythema nodosum. Wallgren[59] observed 3 such cases and found by Addis counts that over one quarter of 88 children with erythema nodosum had an increase in the number of red blood cells in the urine at the height of the eruption. Since erythema nodosum is probably a nonspecific allergic manifestations, and many of the patients have beta-hemolytic streptococci in the throat, the occasional occurrence of glomerular changes is not surprising.

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high incidence of acute glomerulonephritis started in the middle of 1915 and declined after 1916. The disease was largely confined to the men actually fighting in the trenches, the other units of the armies and the surrounding population escaping almost entirely. Men of all ages were equally affected (Maclean[66]), but some German observers state that the disease was more severe in the older soldiers.

In World War II, acute glomerulonephritis seems to have been far less common among the American and British troops than in 1914-18 (a detailed study of 63 cases in Africa and Italy has been published by Brod[67]). The decreased incidence may well have been correlated with less trench warfare. The Germans apparently had considerable "war nephritis" in their winter campaigns in Russia (*cf.* Pilgersdorfer).[68]

Despite extensive investigations (which will be found summarized in Maclean's excellent communication to the Medical Research Committee), the etiology of trench nephritis during World War I was not then regarded as completely elucidated. The fact that the disease was confined to the men in the trenches made it probable that cold, exposure and exhaustion played an important role through predisposing to infection. The disease occurred almost as often in summer as in winter, but men in the trenches are subject to exposure on damp summer nights.

The general manifestations of the disease—epidemic occurrence, generally febrile onset, bronchitic phenomena, frequent splenic enlargement—all pointed to a primarily infectious origin of the disease. Nevertheless, the microörganism responsible was not discovered. Wilson[69] examined bacteriologically the throat, blood, urine and feces in 100 cases without conclusive results. Streptococci, spirochetes, filtrable viruses, and many other organisms were blamed by various investigators. Maclean and others believed the virus might be transmitted by the louse, as in trench fever, for the disease was almost entirely restricted to the men in the trenches, but there was no convincing evidence for this view. The theories put forward that the disease was due to metallic poisoning, avitaminosis, drinking of chlorinated water, etc., were little more than speculations.

From what is now known of the etiology of acute glomerulonephritis, and in view of the identity of the clinical and anatomical pictures of trench nephritis and acute glomerulonephritis in civilian life, there seems every reason to believe that the etiology is the same in both forms, and that the great frequency of acute glomerulonephritis in the trench warfare of World War I was a result of the exposure of life in the trenches predisposing to streptococcic throat infections

The pathological investigations of Dunn and MacNee,[70] Keith and Thomson,[71] Herxheimer[72] and others showed conclusively that trench nephritis was a typical acute diffuse glomerulonephritis, the lesions in the kidney being practically identical with those which are so well known in acute glomerulonephritis in times of peace. In fact, the cases of war nephritis offered the best opportunity ever available for studying the early stages of acute glomerulonephritis, and the anatomical findings will be discussed further below.

Other Infections.—Acute renal disease with hemorrhagic urine may supervene in almost all acute infections—typhoid fever, measles, smallpox,

the seemingly acute glomerulonephritis in the course of one of these diseases is really an acute exacerbation of a chronic process reawakened by the

for the renal mischief. This is especially true in protracted gonococcal bacteriemia. Longcope mentions cases of glomerulonephritis due to the gonococcus, Oettinger, Marie and Morancé[73] have described the occurrence

I have several times seen

carditis due to the gono-

as others, have observed

glomerulonephritis develop in the course of chronic meningococcemia. These forms of acute glomerulonephritis have practically disappeared since the introduction of antibiotics

Judging by the literature, *malarial fever*, a disease with which I have little personal experience, is not uncommonly complicated by glomerulonephritis Descriptions of cases with edema, impaired concentrating ability of the kidneys, and high blood pressure will be found in the monograph of Giglioli[75] His patients were greatly helped by quinine treatment, provided they were not too far advanced at the time the therapy was instituted. The renal complication occurred particularly in long-standing cases. Edema in chronic malaria may, of course, be purely cachectic and without relation to glomerulonephritis (see also p. 658).

In the course of his important anatomical investigations, Bell[76] has published observations which he interprets as indicating that glomerular changes of the same nature as, but of less severity than, those in typical glomerulonephritis occur frequently in a wide variety of infections (puerperal sepsis, tuberculosis, etc) in which clinical glomerulonephritis is extremely rare Baehr[77] points out, however, that the fact that the glomerulonephritis of the clinician is so rare in these diseases bespeaks a fundamental difference between Bell's "subclinical glomerulitis" and clinical glomerulonephritis Moreover, the development of chronic renal disease

sore throat or scarlet fever And the glomerulitis which may complicate almost any infection—here called focal nephritis—and is rarely clinically significant, occurs at the height of the infection, while glomerulonephritis appears after resistance has been developed

Poison Oak and Poison Ivy.—Rytand[78] published several cases of acute glomerulonephritis *and the nephrotic* syndrome in which it seems probable that the renal disease was due to sensitization to poison oak More

recently, Shaffer *et al.*[79] observed 2 patients in whom acute glomerulonephritis followed administration of Rhus Toxicodendron toxin for active treatment of poison ivy contact dermatitis. These observations are of great interest in connection with the allergic nature of acute glomerulonephritis.

Pregnancy.—Pregnancy in its relations to acute glomerulonephritis is discussed in Chapter 32.

Chemicals.—Various chemicals are nephrotoxic. However, the lesions produced by these substances are either nephroses or focal nephritis, and not true glomerulonephritis. I have not seen any case in which definite glomerulonephritis resulted from chemical poisoning, and the failure to produce glomerulonephritis experimentally with chemicals seems to point in the same direction.

Experimental Glomerulonephritis.—The literature of attempts to pro- [illegible] ntally in animals is enormous, but the [illegible] seems unnecessary to review them here. [illegible] of work prior to 1924, Leiter[80] concluded that "Chronic glomerulonephritis has not been produced constantly or even frequently in an experimental animal." Lesions similar in many points to human glomerulonephritis were produced by Christian[81] and his coworkers, Baehr,[82] and others, but they cannot be considered as identical with glomerulonephritis as it occurs in man.

In view of the predominant role of streptococcal infections in the etiology of glomerulonephritis, a number of attempts have been made to reproduce the disease in animals by the injection of streptococci, and their products Pneumococcal autolysates have also been used. With the realization that sensitization plays a fundamental part in the pathogenesis of acute glomerulonephritis, attempts were made to reproduce the disease through immunologic mechanisms These have produced clinical pictures and anatomical changes which at least closely simulate human glomerulonephritis To avoid repetition, consideration of this work will be postponed to the section on pathogenesis (p. 556)

Predisposing Factors.—*Age* —The incidence of acute glomerulonephritis at different ages is a function of the frequency at these periods of the infections which it complicates Because of the important role of scarlet fever and angina in the etiology of acute glomerulonephritis, it is most common in childhood. It may occur during earliest infancy; 3 of Clausen's[83] 102 patients with acute glomerulonephritis developed in the first year of life. Rennie[84] reported 10 cases in infants less than eighteen months of age, and I have seen several. However, before the age of three, chronic nephrosis is more common than glomerulonephritis. Next to childhood, the greatest incidence of the disease is in adolescents and young adults, in whom it most commonly follows tonsillitis and other forms of angina Acute glomerulonephritis is rare in the aged, but I have once seen the first attack after sixty years of age

A few cases have been observed which indicate that, on extremely rare occasions, glomerulonephritis develops *in utero (congenital nephritis).* Karsner[85] describes a diffuse proliferative lesion of the glomeruli in an infant who succumbed forty-five minutes after birth. He also quotes 3

other cases *from the literature*, in 1 of which anasarca develops the day after birth and chronic renal disease was later found at necropsy. Thompson[1??] found subacute to chronic glomerulonephritis in an infant who succumbed at twenty-nine days; the mother had had pharyngitis in the sixth month and the possibility of intrauterine sensitization to organisms in the mother was considered. Dr. Chester Brown has shown me the kidneys of an infant who died at the age of four months with glomerulonephritis that had already attained the subchronic stage; the process must have had its inception either before or shortly after birth.

Sex.—Dickinson[86] found that of 105 cases in children, 58 were in boys and 47 in girls, while of 54 cases in adults, 33 were in males. Murphy and Rastetter[87] and Seegal, Seegal and Lyttle[88] found an even greater predominance of males. *The higher incidence in adult males is perhaps due to their greater exposure to cold and wet* with resultant tonsillitis and other infections.

Familial Occurrence.—A number of instances have been recorded in which [illegible] the same family, either w [illegible]

Eason [illegible]

acute glomerulonephritis within a relatively short period. [illegible] and Robb[90] observed a familial epidemic in which, in quick sequence, an upper *respiratory infection was followed by glomerulonephritis in 6 of 10 brothers* and sisters. Rinkoff et al.[91] followed three brothers who succumbed to uremia, in all of whom necropsy revealed chronic glomerulonephritis. I [illegible] family in which three brothers at long intervals de-

[illegible]

basis of allergy, or of a common throat infection by a particular type of streptococcus (p. 546).

Epidemic Occurrence.—Epidemic occurrence of acute glomerulonephritis was observed during World War I as the so-called trench nephritis. Epidemics, apparently small, of the disease were noted in civil life by Tallqvist.[92] An epidemic of acute glomerulonephritis was observed in Amsterdam by Formijne,[93] and of 17 cases within three months in a mental hospital by Molony.[94] In certain years, postscarlatinal glomerulonephritis occurs in a far higher proportion of cases of scarlatina than in others (p. 532). In New York City the number of cases of acute glomerulo-

[illegible]

been highly esteemed as an etiological factor in renal disease [illegible] old has ... The combination of cold and wet, as being drenched in a cold rain, wet feet in cold weather, or falling into water, seems *particularly apt to* incite acute glomerulonephritis. Exposure to cold when intoxicated is often mentioned in the older literature as being followed by renal disease. In New York

City I have observed that glomerulonephritis is more common in individuals whose occupation exposes them to inclement weather and in the children of the poor. But since the advent of the bacteriological era, it has become more and more evident that cold, wetting and other varieties of exposure do not in themselves produce glomerulonephritis, which is always primarily the result of an infection. In the large majority of patients in whom there is a history of exposure to cold previous to the development of acute glomerulonephritis, sore throat or other evidence of respiratory infection is present. But even if angina, rhinitis, sinusitis, etc. are not demonstrable, infection has doubtless occurred and subsided before the renal disease became evident; there is usually a period of about ten days between the sore throat and the appearance of manifestations of glomerulonephritis. In typical instances of glomerulonephritis following exposure, streptococci have been demonstrated in the urine (Luedke,[97] Loehlein[98]) even though sore throat or another infectious focus was not observed. The changes in the kidneys are identical in those cases of acute glomerulonephritis with a definite history of antecedent infection and in those in which this is not obtained. It seems definite, therefore, that the renal disease in the latter group also results from an infection and that cold or other exposure participates through creating a predisposition to this infection.

The experiments of Mudd and Grant[106] are of interest in this connection. They found by accurate methods that "chilling of the body surface causes reflex vasoconstriction and ischemia in the mucous membranes of the palate, faucial tonsils, oro-pharynx and naso-pharynx." They believe it not improbable that "the ischemia of the mucous membrane resulting from cutaneous chilling might so disturb the equilibrium between the host and the bacteria in the tonsillar crypts and folds of the pharyngeal mucosa as to excite infection." A working hypothesis of the role of cold in predisposing [illegible] that the reflex ischemia of [illegible] antecedent and causative infection.

Attempts have also been made, particularly by investigators of previous generations, to show that exposure to cold may have a more directly deleterious effect on the kidney. There seem to be rather close interrelations between the cutaneous and renal circulations Cohnheim and Roy,[99] Wertheimer,[100] and others found experimentally that chilling of the skin produces vasoconstriction followed by vasodilatation in the kidney; i. e., the same reactions that occur in the skin. Affanassiew[77] and others long ago found that chilling the skin of animals often results in renal lesions. Similarly, Johnson[101] noted that cold bathing is frequently followed by transitory proteinuria. It would seem that large areas of the cutaneous surface must be chilled to result in proteinuria, for Chodounsky, Boucek and Polak[102] were unable to produce proteinuria by immersing their legs up to the knees for from ten to twenty minutes in water at a temperature of from 3.5° to 6.1° C. Siegel[103] claimed to have produced "parenchymatous nephritis" in dogs by immersing their hind legs in water at 4° C. for ten minutes, but his results were not confirmed by Polak,[104] who did not observe even proteinuria if the dogs were prevented from assuming a lordotic position during the exposure. Siegel and Gaisboeck[105] have pro-

course, the results of such coarse experiments can have no significance for
the study of renal disease in man
that exposure of the body to

Trauma —The kidney
temuria not uncommon
palpatory albuminuria
but, as he apparently re
of the forms of Bright's disease. Since then, numerous cases have been
sometimes with edema, has been

trauma is doubtless a coincidence, and it must be left an open question whether trauma actually predisposes to glomerulonephritis.

BACTERIOLOGY OF ACUTE GLOMERULONEPHRITIS

The preponderant role of infection by streptococci in the etiology of acute glomerulonephritis is obvious from the diseases which it most commonly complicates—scarlet fever, sore throat, subacute bacterial endocarditis—the first of which is always due to streptococci, and the last two almost invariably Infected wounds and localized suppurations which are followed by true glomerulonephritis practically always contain streptococci, either as the primary cause or as secondary invaders. Also, the infectious purpuras, which are not uncommonly complicated by acute glomerulonephritis, are at least often due to streptococci On rare occasions, glomerulonephritis complicates rheumatic fever, which seems to be a manifestation of streptococcic infection. In acute glomerulonephritis following exposure to cold, streptococci have several times been demonstrated in the urine, in such cases an undetected streptococcic infection of the throat was probably present For these reasons, beginning more than three

for acute glomerulonephritis. Further evidence of the role of streptococci in the causation of glomerulonephritis is afforded by Longcope's demon-
iltrates and aug-
. The variegated
coccic etiology of
and Weaver ... of Rammelkamp

onephritis is
throat infec-
endocarditis due

vorkers demonstrated
7 per cent and Streptococcus viridans in 12.7 per cent of their cases of glomerulonephritis. Evidence has recently been adduced that among Group A hemolytic streptococci, certain immunologic types are especially apt to produce glomerulonephritis. Typing by the precipitin method of Lancefield, Rammelkamp and Weaver[113] found that 26 of 31 attacks of acute glomerulonephritis were due to Type 12. Confirmation of these observations was obtained by Wertheim *et al.*,[114] who observed that 51 per cent of the type-specific hemolytic streptococci isolated from throat cultures in various stages of glomerulonephritis belonged to Type 12.

While there is no doubt that streptococcic infections are responsible for the vast majority of instances of glomerulonephritis, the nature of the connection is obscure. Why, for instance, are some streptococcic infections followed by rheumatic fever and others by glomerulonephritis? It is rare for both to occur in the same patient, but when the rheumatic cardiac later develops subacute bacterial endocarditis glomerulonephritis may complicate the picture. Nor do we know why some very mild streptococcic infections are followed by glomerulonephritis, while other severe infections with bacteremia and passage of many organisms through the kidney into the urine are not accompanied by renal lesions. Thus, in puerperal sepsis and erysipelas, streptococci are often present in the urine, and may be found post mortem in the kidneys, but glomerulonephritis is rare In the cases of tonsillar sepsis that I have seen, glomerulonephritis has been absent, while very mild tonsillitis may produce the disease. Nor does adequate and seemingly successful treatment of streptococcic sore throat necessarily prevent the subsequent development of glomerulonephritis. Rammelkamp and Weaver believe that the answer to some of these questions lies in the existence of strains of streptococci which are especially "nephritogenic." In
Type 12 streptococci
widely varying incide
in different years, and
family groups, schools, military installations, etc. I have also seen a very few instances of multiple occurrence of glomerulonephritis in a family (usually years apart), but they have been too few in number to be interpreted as more than coincidental. However, the possibility that certain types of streptococci are more apt than others to produce nephritis is plausible and worthy of further investigation. The problem of the role of the host in the relation between the infectious focus and glomerulonephritis is considered below in the section on pathogenesis

In connection with the role of streptococcal infection in chronic glomerulonephritis, an interesting point has been brought out by Seegal, Seegal and Lyttle.[88] They found that the admission rate for glomerulonephritis is about the same in hospitals in the South and in the North of the United States. It has been established that the admission rate for rheumatic fever and scarlet fever—two diseases in which hemolytic streptococci are concerned and which present other analogies with glomerular nephritis—is much less in the southern hospitals. The reason for this difference is ob-

This is proven by cases of sub-
nic bacteriemia due to these
which true glomerulonephritis

ng the possibility that products
of the tubercle bacillus may cause glomerulonephritis, will be further discussed below

While it is very possible that other microörganisms are rare causes of
... this has not been proved. The

that the specific virus of each disease is responsible ...
these may be due to secondary infection with streptococci.

PATHOLOGICAL ANATOMY OF ACUTE GLOMERULONEPHRITIS

though these are often minimal and not always characteristic.

The kidneys are of normal size or enlarged, each weighing 200 grams or more. Observations during decapsulation operations indicate that the kidneys are often larger during life than they appear at postmortem examination. The consistency is generally softer than normal. The capsule strips readily and without loss of substance, revealing a surface which is pale-grayish-brown or reddish-brown in color. Deeply congested kidneys which drip blood on section are sometimes encountered where venous stasis was present during life. In early cases the color tends to be pale, in later cases darker. The stellate veins are often injected. Tiny hemorrhagic points and streaks are usually but *not always found.*

On section, as a rule, the cortex and medulla are well delimited from one another, the medullary pyramids being deeply congested and much darker than the cortex. In very early cases the kidney substance looks much as

sometimes more prominent than normally, *appearing* either as pale, translucent and grayish, or else as dark red, points; in other instances, they are hidden by the swollen parenchyma. There may be jagged hemorrhagic

kidneys. The cases of
I others) are based on
... adequate anatomical evidence.

Microscopic Picture.—Though many of the essential microscopic chang in acute glomerulonephritis were described by Klebs,[1] the first adequat histological description was given by Langhans[2] in 1879. His observation were greatly amplified by Loehlein[3] and by investigations on very earl cases of trench nephritis during World War I, notably by Dunn and Mac Nee[70] and Herxheimer.[72] The study of McGregor[116] with the aid of specia staining methods has clarified knowledge notably; in her paper, and the subsequent one of Bell[117] from the same laboratory, will be found an exhaustive survey of the pathological histology of acute glomerulonephritis.

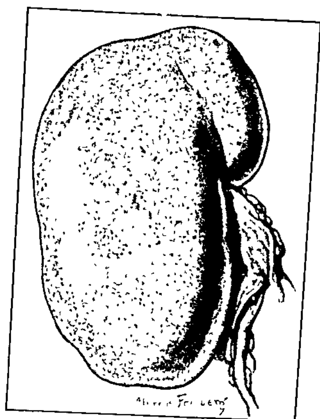


FIG 24.—Acute glomerulonephritis The kidney is swollen and its surface dotted with punctate hemorrhages

The Glomeruli.—From the above and other researches, it is now known that *the first lesions involve the capillary loops of the glomeruli, consisting in endocapillaritis.* During World War I, Herxheimer studied 13 cases of acute glomerulonephritis that died at very early stages of the disease, 5 in from one to three days after the first symptoms. He found the initial changes to consist in dilatation of the capillary loops, which are mostly devoid of blood and filled with a "coagulated protoplasmic exudate" continuous with the capillary wall. The *extreme ischemia of the glomeruli* is also emphasized by Dunn and MacNee on the basis of 35 cases of trench nephritis. They found that in many kidneys of such cases, not more than one or two loops in any section of a tuft contain red blood cells The

ischemic loops are largely filled by cellular and other content, which de-

Individual capillaries may be lined with several ... the endothelial cording ... is as though many of the endothelial cells a ... study ...



Fig 25.—Acute glomerulonephritis. The glomeruli are almost completely ischemic due to blocking of the loops by swelling of the endothelial cells and cellular proliferation. The tubules are filled with albuminous fluid and there is blood in some. (Same kidney as Fig 24.)

case—which is so rarely seen at necropsy in civil life—the endothelial

the lobules. *Accompanying the proliferation of the fixed elements* is an

* In ordinary necropsy material mitoses are very rarely demonstrable in glomeruli. However, by examining kidneys fixed thirty and *forty-five minutes after death*, Hartz et al demonstrated mitotic divisions in the endothelial and epithelial cells in acute and subacute glomerulonephritis.

Microscopic Picture.—Though many of the essential microscopic changes in acute glomerulonephritis were described by Klebs,[1] the first adequate histological description was given by Langhans[2] in 1879. His observations were greatly amplified by Loehlein[3] and by investi... on very early ... unn and Mac- ... aid of special staining methods has clarified knowledge notably; in her paper, and the subsequent one of Bell[117] from the same laboratory, will be found an exhaustive survey of the pathological histology of acute glomerulonephritis.

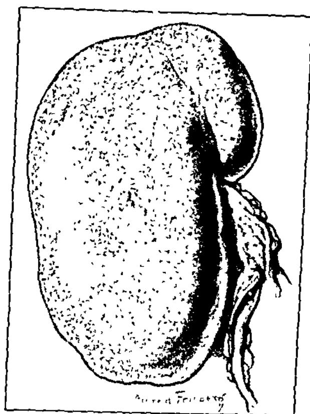


FIG 21 —Acute glomerulonephritis. The kidney is swollen and its surface dotted with punctate hemorrhages

The Glomeruli.—From the above and other researches, it is now known that *the first lesions involve the capillary loops of the glomeruli, consisting in endocapillaritis.* During World War I, Herxheimer studied 13 cases of acute glomerulonephritis that died at very early stages of the disease, 5 in from one to three days after the first symptoms. He found the initial changes to consist in dilatation of the capillary loops, which are mostly devoid of blood and filled with a "coagulated protoplasmic exudate" continuous with the capillary wall. The *extreme ischemia of the glomeruli* is also emphasized by Dunn and MacNee on the basis of 35 cases of trench nephritis. They found that in many kidneys of such cases, not more than one or two loops in any section of a tuft contain red blood cells. The

The thickening leads to fusion of individual loops, so that the appearance ... network containing many

...

ment membrane and form a network ...
thrombosis may occur.

These intracapillary and extracapillary changes lead to enlargement of the tuft, so that it completely fills the capsular space and may protrude hernia-like into the proximal convoluted tubule. According to the measurements of Langhans, the glomerulus may attain a diameter of 0.30 or 0.35 mm.

... of Herxheimer, the epithelium of Bowman's ... fatty change. Proliferation and ... ge. But even in the earliest cases there may be hemorrhage into varying numbers of the capsular spaces, which may also contain leukocytes, coagulated protein, and fibrin.

While the glomerular epithelium may show no morphological evidences of damage in the earliest stages, it has nevertheless been severely damaged. This is shown by the presence of albuminous exudate and red cells in the capsular spaces, as just mentioned. Further evidence of damage to the epithelial cells of the glomerulus in the early stage was found by Langhans; his description is translated here because of the importance of the findings for the pathoge... of proteinuria in such cases: "If one examines the epithelium of a ...
(i e, by teasing ...
flamed kidneys, ...
... ... so easily in large shreds, but

...

has, therefore, become less through solution of the uniting cement substance, perhaps also, they are not so strongly attached to the capillary loops" It is easy to see how protein can pass through the damaged capillaries and such a loosened epithelium into the capsular space, resulting in proteinuria

Even in the earliest stages, *almost all the glomeruli are involved*, a fact which was already noted by Langhans and strongly emphasized by Loehlein Kuczynski[121] has communicated observations on renal complications of influenza which he believes to indicate that diffuse glomerulonephritis may start as a focal process, but all other studies demonstrate that the disease is almost diffuse from the start (Dunn and MacNee,

...

hematuria results

accumulation of polymorphonuclear leukocytes within the glomerulus. This was studied by Graeff[119] by means of the oxydase reaction. He found that while in sections 15 microns thick, the normal glomerulus contains from 3 to 25 leukocytes, in acute glomerulonephritis this number is increased and may even reach 100. In later stages, the number of leukocytes declines. The result of the cellular proliferation and accumulation is that the entire glomerular tuft is much more thickly beset with nuclei than normally (*Kernreichtum* of the Germans), which is often very striking in the first glance at the section under the low power.

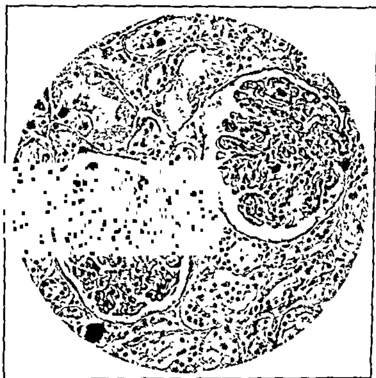


Fig 26.—Acute glomerulonephritis Swelling of the capillary walls and ischemia of the loops

In the foregoing, the increase in the number of nuclei in the glomerular tuft which characterizes the early stages of acute glomerulonephritis has been described as due to the proliferation of endothelial cells and accumulation of leukocytes within the capillary loops, i e, an intracapillary process. MacCallum championed the view that the nuclei in question arise from proliferation of connective tissue cells between the loops, i e, an intercapillary process Jones[173] also believes that most of what has been regarded as endothelial proliferation in glomerulonephritis is actually migration of histiocytic cells into the interstitial spaces of the glomerulus However, other evidence (see Bell) indicates strongly that the proliferation is actually initiated within the basement membrane of the capillary endothelium.

The normally delicate walls of the glomerular loops become thickened and appear hyaline or, in other instances, somewhat granular; inasmuch as McGregor found little change in the basement membrane in the early stages, this change is probably largely due to swelling of the lining cells.

of epithelial crescents makes its appearance. The tubular epithelium undergoes regressive changes. There is broadening of the interstices with accompanying interstitial infiltration. The appearance of these changes [illegible] the transition to the subacute stage and will be discussed in detail

[illegible]

in which death occurred from some comp[illegible] been studied by Fahr[127] and others. The process of healing evidently starts with regression of the thickening of the walls of the loops and removal of the exudate which block the glomerular capillaries following [illegible] the previously ischemic capillaries become congested with blood. [illegible] that improvement in acute [illegible] n increase in the hematuria. [illegible] ithout leaving any damage whatsoever is known from necropsies on individuals who have had the disease and die from some other cause years later, without there being any evidence of the previous inflammatory process. In other instances, of course, healing is accompanied by obliteration of a greater or lesser number of glomeruli.

Summary.—Acute glomerulonephritis is a diffuse endocapillaritis of the glomerular loops. Its fundamental histological features are swelling and proliferation of th[illegible] [illegible]thelial cells of the glomerular capillaries and accumulation of inf[illegible] Marked ischemia [illegible] ular capillaries thus produced [illegible] epithelium, but this apparently starts subsequent to the endocapillary changes. Even in the earliest cases studied, the process is very diffuse, sparing only isolated glomerular loops. Tubular lesions of consequence are not present in the earliest stages, only appearing later. In very severe cases, there may develop in later stages inflammatory and necrotizing lesions of the vasa afferentia.

PATHOGENESIS OF ACUTE GLOMERULONEPHRITIS

[illegible]

renal lesions that appear three weeks after the onset of the scarlatina, when the patient has often been afebrile for two weeks or more, and is seemingly completing his convalescence? Satisfactory answers to these questions cannot as yet be given, but much relevant data has been accumulated in recent years.

Direct bacterial invasion of the kidney from the primary focus *via* the blood stream is highly improbable. True glomerulonephritis is very rare in puerperal and other forms of sepsis—including tonsillar sepsis and early septic scarlet fever—despite the fact that the blood teems with highly virulent streptococci or other bacteria and the urine may contain large numbers of the organisms. The forms of renal disease present in such

The Tubules and Interstices.—In the early stages, the epithelial cells lining the tubules are little changed. There may be slight cloudy swelling or fatty change, but even this is sometimes absent. The tubules in the cortex are often dilated. In the lumen of the tubules are casts, erythrocytes, coagulated exudate, leukocytes, and exceptionally hemoglobin from laked red cells.

There are no interstitial changes in the early phases, apart from intertubular edema of varying degree and occasional leukocytic infiltrates around the glomeruli. The intertubular capillaries are usually dilated and filled with blood, in sharp contrast to the findings in the glomerular capillaries. Their walls, moreover, show no changes comparable to those in the glomerular capillaries, though occasionally the endothelial cells are somewhat swollen.

The Arteries.—In early cases the arteries appear normal in the usual examination of the sections. However, Kuczynski[122] has found by detailed study of serial sections that some, though not all, of the vasa afferentia exhibit such changes as edematous swelling, vacuolization and slight cellular infiltration of the wall close to the entrance into the glomerulus. These changes apparently are but slight. But in the later acute and early subacute stages of glomerulonephritis, there may appear severe inflammatory and necrotizing lesions of the arterioles which were first described by Loehlein[123] and have since been studied by Baehr and Sacks[124] and Jaffe.[125] I[126] found these lesions in 3 of 8 cases of later acute glomerulonephritis; in one of them, the renal process was evidently less than three weeks old. The lesions consist essentially in a necrotizing arteriolitis of the vas afferens just previous to its entrance into the glomerulus, often accompanied by thrombotic occlusion of the lumen which may be projected into the first glomerular loops. I have seen small necroses of the glomerular capillaries accompanying the necrosis of the vasa afferentia In some of Loehlein's cases, the necrosis of the arteriolar walls was so severe that tiny aneurisms were formed with extravasation into the surrounding tissues. In all the cases in which I found necrotizing arteriolitis the renal process was very severe with death from renal insufficiency. It is to be emphasized that the necrotizing arteriolitis is not found in the earliest stages, and when present involves only a fraction of the vasa afferentia; it cannot, therefore, be regarded as the cause of the glomerular lesions. Thrombosis of isolated arterioles is occasionally present

It does not seem probable that the necrotizing arteriolitis of later acute and early subacute glomerulonephritis has any relation to the endarteritis and arteriolosclerosis found in the chronic stages of the disease (Chapter 21) The acute arteriolar lesions occur, so far as is known, in only very severe renal processes, and it i [illegible]
on to the chronic stage [illegible]
occur in many cases in [illegible]
of the type in which necrotizing arteriolitis is present.

Chronicity and Healing.—If the patient does not improve and the renal process progresses after the first few weeks, other changes appear. Thickening and hyalinization of the glomerular loops become more prominent, and in some cases proliferation of the capsular epithelium with the formation

process of immunization. A similar line of thought was followed by Long-

1. The fact has already been mentioned that glomerulonephritis com-
plicating tonsillitis or scarlet fever develops not at the height of the infection but during convalescence when the symptoms of the primary disease are receding or have disappeared altogether.

2. Clinical manifestations much akin to those of glomerulonephritis are not uncommon in serum sickness. Thus, Mackenzie and Hangar[132] state that: "Edema occurs in about one-third of all the cases (of serum disease), and it has the distribution of nephritic edema. With the edema there is chloride and water retention, a lowered phenolsulphonphthalein excretion, diminished volume output, albuminuria and cylindruria, with rarely, if ever, a demonstrable nitrogen retention. The impaired renal function is, so far as we know, always transitory." Longcope and Rackemann[133]

albuminuria, cylindruria, increase in blood urea, profound depression of the index of urea excretion, decrease in the output of phenolsulphonphthalein and retention of chlorides and water."

3 Longcope[134] and his coworkers have studied the skin reactivity to filtrates of cultures of hemolytic streptococci recovered from tonsillar and

4. Friedemann and Deicher[135] found that the blood of patients with postscarlatinal glomerulonephritis contains far more antibodies than that of scarlatinal convalescents of the same period without glomerulonephritis But they did not find a high antibody content in the serum of scarlatinal patients with septic complications. They, therefore, concluded that premature antibody formation in patients with postscarlatinal glomerulonephritis is a cause of the renal mischief. Likewise, Longcope[146] found that in cases of acute glomerulonephritis of abrupt onset following a severe throat infection or scarlet fever, the titer of the blood in antistreptolysin (antibody against streptococcal hemolysin) rises to high levels. The same is true of rheumatic fever, another disease in which there is good reason to suspect sensitization to streptococci

Recently, Lange[147] and his coworkers have found that the serum *complement* level is low in active glomerulonephritis. *Lange had previously* found antibodies to human kidney in the serum in *glomerulonephritis* and attributes the low level of complement to a *complement-binding* antigen-antibody reaction.

5 Diffuse glomerulonephritis *occurs much more often in Libman's* bacteria-free and healed stages of subacute bacterial *endocarditis than* when the patient succumbs during *the stage of demonstrable bacteremia.*

cases are abscesses, focal nephritis, acute interstitial nephritis, or merely febrile proteinuria. On the other hand, numerous investigators have shown that the blood and urine are almost always sterile in patients with glomerulonephritis. Wilson[69] found this to be the case in trench nephritis and Longcope[5] and his coworkers in various forms of glomerulonephritis in civil life. Friedemann and Deicher[128] were unable to demonstrate microorganisms by culture of the urine of 11 patients in the acute stage of postscarlatinal glomerulonephritis, though 1 of the 11 urines did yield a pure culture of the scarlatinal streptococcus on intraperitoneal inoculation into mice. It is true that streptococci have been found in some instances in the kidneys. However, in the majority of cases of acute glomerulonephritis organisms cannot be demonstrated in the kidneys. Thus, Bell and Hartzell[4] were able to find them in but 1 of 11 cases. Those exceptional cases in which bacteria are found in the kidneys or urine do not indicate that the organisms found locally are necessarily the cause of the renal lesions, for bacteria are often found in the kidneys of patients who had bacteriemia without any glomerulonephritis whatsoever.

These findings showed that the cause of glomerulonephritis is not the actual invasion of the kidneys by microörganisms. The conception that next found favor was that *the renal process is the result of injury by a toxic substance.* The diffuse nature of the glomerular injury, also seemed to speak in favor of the toxic nature of the process.

This conception of the toxic origin of glomerulonephritis appeared to be decidedly fortified by the discovery of the scarlatinal streptococcus with its powerful toxin by the Dicks and Dochez, and the demonstration that the rash and other symptoms are due to the toxin. Longcope and his coworkers also found that streptococci from infectious foci in patients with glomerulonephritis produce toxic filtrates which are often of considerable potency. Trask and Blake[129] demonstrated the presence of the toxin of the scarlatinal streptococcus in the urine of 2 of 5 patients with scarlet fever. On the basis of these and similar findings, the conception arose that the streptococcic infections responsible for glomerulonephritis damage the kidneys through the intermediacy of toxins which injure the glomerular capillaries during excretion.

But the pathogenesis of acute glomerulonephritis is doubtless more complicated than direct injury to the glomerular and other capillaries by the unaltered circulating toxic products of the microörganisms of the primary disease. Such a conception would scarcely explain the remarkable fact that postscarlatinal glomerulonephritis appears during convalescence and not at the height of the disease when the fever, rash and other symptoms demonstrate the presence of the scarlatinal toxemia. A similar sequence of events occurs in glomerulonephritis of tonsillar origin. Formerly, it was thought that desquamation following scarlet fever affords an opportunity for injury to the kidneys as a result of chilling of the skin, but there is no evidence in favor of this view. Following the first studies on serum sickness and other allergic phenomena, Schick[130] pointed out the analogy of the course of events in these conditions with the latent period between scarlet fever and postscarlatinal glomerulonephritis, and suggested that *the renal complication depends on the development of a hypersensitive state in the*

I pneumo-
of pneumo-
with edema

ducing glomerular lesions when the living cultures ...
immunized rabbits And if they liberated the endotoxic substance of the
... peritoneal cavity of an immunized
homologous
An attrac-

sickness" (arthritis, adenitis, etc) Duval and Hibbard designate the
lesions they produced as glomerulonephritis, but whether they are identical
with the lesions in the human disease requires further study It is further
worthy of note that Duval and Hibbard found that when they induced a
general infection of the animal with scarlatinal streptococci, *the renal*
lesion was acute interstitial nephritis and not a glomerular change. These

(c) Long and Finner[143] found that the injection of tuberculin into the
renal artery of non-tuberculous swine did not produce glomerular lesions.
But if the animals was previously sensitized by a mild tuberculous infection,
the same procedure was followed by glomerular changes. Here, again,
further study is required to demonstrate if the lesions are entirely identical
with human diffuse glomerulonephritis

(d) A very interesting experiment has been reported by Bell and Clawson[144] Over a period of four years they injected suspensions of a culture of
Streptococcus viridans into the veins of a monkey The animal developed
persistent proteinuria and frequent hematuria but no edema or hyper-

in the thickness and number of layers of the capillary basement membrane" These findings indicate that Bell and Clawson produced a renal
lesion at least closely simulating if not identical with human glomerulonephritis Furthermore, the long duration of the experiment lends strong
support to the *theory that sensitization* plays an important part in the
pathogenesis of glomerulonephritis

One-third of Libman's[27] bacteria-free and healed cases died of uremia, while the proportion of "active" cases that have this termination is exceedingly small. This theoretically and practically important fact has been established by the extensive studies of Libman and Baehr cited on p. 533. The entrance of a patient with subacute bacterial endocarditis into the bacteria-free or healed stages is, of course, evidence that the processes of immunization are active and have met with some success.

It was mentioned above that glomerulonephritis may develop in long-standing bacteriemia due to the gonococcus, pneumococcus, meningococcus or influenza bacillus. I have the impression from my own experience and from the literature that glomerulonephritis is less rare in such protracted infections than in acute infections due to the same organism; but I am unable to cite sufficient material to advance this statement as more than an impression except in the case of the gonococcus. In prolonged gonococcal bacteriemia, the development of glomerulonephritis seems to be the rule and not the exception.*

Perhaps in analogy to the considerable incidence in subacute bacterial endocarditis, Lillehei[138] and his associates have observed glomerulonephritis in one-third of dogs in which arteriovenous fistulas had been created six weeks to five months before. They have been able to produce glomerulonephritis and endocarditis in dogs with such fistulas by the injection of relatively small numbers of Beta Hemolytic Streptococci or Streptococcus Viridans. How the "cardiovascular stress" due to the arteriovenous fistulas abets the bacteremia in the production of the glomerulonephritis and endocarditis remains to be determined.

6 A number of attempts have been made to produce glomerulonephritis experimentally in sensitized animals.

(*a*) The first work along this line was that of Longcope.[131] He was able to produce renal lesions in dogs, rabbits and other animals by repeated injections of horse serum and egg-white, among which were marked glomerular changes.

Subsequently, this line of investigation was pursued in detail by Longcope[139] and his pupils By the injection of suspensions of heat-killed hemolytic streptococci into the renal artery of rabbits, Lukens and Longcope were able to produce glomerular lesions in about one-half the animals used. The glomerular lesions were much more frequent in rabbits in which an acute localized infection had previously been induced by the intracutaneous injection of living streptococci than in normal animals The occurrence of acute glomerulitis was generally associated with a well-marked skin reaction to filtrates of hemolytic streptococci. The glomerular lesions were apparently not diffuse and, as pointed out by Lukens and Longcope, are not to be considered as strictly analogous to human glomerulonephritis. McLeod and Finney[140] produced similar lesions by the injection of suspensions of Streptococcus viridans into the renal artery. Further experiments have been reported by Blackman, Brown and Rake.[141] They produced what they term "characteristic acute and subacute

* Dr George Baehr informs me that he found glomerulonephritis in 5 of the last 6 cases of gonorrheal endocarditis that came to necropsy at Mount Sinai Hospital (before the days of penicillin).

toxin.* They were able to prevent renal damage by preceding the injection of this serum by an intravenous injection of saline extract of rat kidney. Presumably, the rat-kidney extract combines with the *anti-rat-kidney serum* and thereby prevents the nephrotoxic action of the latter. In interesting analogy with the interval between the causative infection and the development of glomerulonephritis in man, experimental nephrotoxic [illegible] following the injection. Sarre[illegible]

[illegible]

normal proteins of the injected duck serum, [illegible] bination of the injected duck antibody-rabbit kidney combination now functioning as an antigen. This secondary interaction results in nephritis, which therefore does not appear until the rabbit has had time to form *antibodies to duck proteins.* Kay's findings accord with the hypothesis that human glomerulonephritis results from the interaction of antibodies with an *antigen formed by the action* of some product of streptococcic [illegible] the kidney.

[illegible]

least closely related to glomerulonephritis is at least in excellent harmony with the conception that sensitization to bacterial infection and the mechanisms concerned in the development of resistance to infection are in some obscure way concerned in the pathogenesis of human glomerulonephritis.

Parenthetically, it may be mentioned that Hepler and Simonds,[144] working along the line of the Arthus phenomenon, have produced "anaphylactic inflammation" in the kidneys of rabbits. They sensitized rabbits by repeated subcutaneous injections of a protein and then injected the protein directly into the kidney. A severe hemorrhagic and necrotizing inflammation resulted, but the description reveals no morphological analogies to glomerulonephritis.

(*f*) *Production of Glomerulonephritis by Autoantibodies.*—Cavelti and Cavelti[145] found that treatment of an emulsion of rat kidney with killed group A streptococci renders the kidney material antigenic in the same species. By *immunization* of rats with such a mixture, they *produced* antibodies to rat kidney and glomerulonephritis. They bring evidence that

[illegible]

anti-rat-placenta serum [illegible] may be produced by injections of rabbit [illegible]

(c) *Production of Glomerulonephritis with Anti-kidney Serum.*—By the injection of anti-kidney serum, Masugi[145] produced a very close simulation of human glomerulonephritis. His results have been confirmed and extended by Smadel, *et al.*,[146] Arnott *et al*,[147] and others. Masugi found that if a rabbit is repeatedly injected with a suspension of rat's kidney, subsequent injection of the rabbit's serum into a rat produces a clinical and anatomical picture closely resembling that of human glomerulonephritis. Arnott and his associates prepare[illegible]
of rabbit kidney into a
et al. prepared an anti-
changes in the dog similar to those produced by nephrotoxic sera in the rat and rabbit.

The clinical picture produced by the injection of the anti-kidney serum is characterized by proteinuria, cylindruria, renal insufficiency with azotemia, hypoproteinemia, lipemia, and hypertension. While hematuria often occurs, Smadel found that it is part of an anaphylactoid reaction and is not due to the specific nephrotoxin. Smadel and Farr produced rapidly fatal nephritis by injecting relatively large amounts of antikidney serum at frequent intervals and a chronic type, of duration of even a year, by giving small quantities in single or repeated dosage. Farr and Smadel made interesting observations regarding the relation of the diet to the course of experimental nephritis. They found that 13 of 15 rats which were given a low-protein diet after a single injection of anti-kidney serum had recovered within eight and a half months On the other hand, 8 of 15 similarly injected rats which were given a high-protein diet died of renal failure within five and a half months and 6 of the remainder were definitely abnormal.

Anatomically, the injection of the anti-kidney serum is followed by changes in the glomeruli and tubules. The basement membrane of the glomerular loops becomes thickened and there may be swelling of the endothelial cells. The degree of proliferation of the endothelial nuclei varied in different observations. There is proliferation of the capsular epithelium with the formation of crescents. With longer duration of the process, connective tissue proliferation converts the glomerulus into a scar. Thrombosis of glomerular loops may occur, but is attributed by Smadel to an anaphylactoid reaction not due to nephrotoxin alone The tubules undergo various regressive changes which may attain necrosis; there are areas of tubular dilation and the formation of casts. Interstitial fibrosis develops. When the lesion is present for a long time, Smadel describes widespread vascular lesions (arteriolar thickening, hyalinization, fatty change, fraying of the internal elastic membrane, calcification) with areas of secondary degeneration in various organs. Cardiac hypertrophy may develop in such instances

It is evident that these investigators have produced a remarkable simulation of human glomerulonephritis. But the mechanism of nephrotoxic nephritis is not simple and by no means completely understood. Swift and Smadel showed that the effect of the anti-kidney serum on the kidney is dependent on a relatively organ specific antibody called nephro-

toxin.* They were able to prevent renal damage by preceding the injection of this serum by an intravenous injection of saline extract of rat kidney. Presumably, the rat-kidney extract combines with the anti-rat-kidney serum and thereby prevents the nephrotoxic action of the latter. In i ... with the interval between the causative infection and

[illegible]

... idate these findings by ...

serum. This ...
kidney in the ...
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bination of the injected duck ... functioning as an antigen. This secondary interaction results in nephritis, which therefore does not appear until the rabbit has had time to form antibodies to duck proteins Kay's findings accord with the hypothesis that human glomerulonephritis results from the interaction of antibodies with an antigen formed by the action of some product of streptococcic infection on the kidney.

But the significance of the experiments for the pathogenesis of the human disease remains to be determined. In any event the demonstration that antibodies can be produced which damage the kidney in a fashion that is at least closely related to glomerulonephritis is at least in excellent harmony with the conception that sensitization to bacterial infection and the mechanisms concerned in the development of resistance to infection are in some obscure way concerned in the pathogenesis of human glomerulonephritis.

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[illegible]

repeated subcutaneous injections ... directly into the kidney A severe hemorrhagic and necrotizing inflammation resulted, but the description reveals no morphological analogies to glomerulonephritis

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[illegible]

anti-rat-placenta serum. ...

the renal lesions are due to the action of the antibodies on the kidney. If action of products of human streptococcic infection on kidney were similarly demonstrated to evoke antibodies to kidney, a very appealing explanation of the pathogenesis of glomerulonephritis as due to effects of these antibodies on the kidney would be presented. However, Humphrey[156] was unable to reproduce Cavelti's results.

(*g*) *Globulin Glomerulonephritis.*—Recent experiments indicate that glomerulonephritis can be induced by injection of serum globulins. Haun and Janeway[157] accomplished this in rabbits by a single injection of purified bovine serum gamma globulin; the lesions were most marked a week after injection. More and Waugh[158] produced a high incidence of glomerulonephritis in unilaterally nephrectomized rabbits by two successive doses of purified serum gamma globulin. The lesions were closely similar to human acute and subacute glomerulonephritis. McClean[159] and his associates caused glomerulonephritis in rabbits by daily intravenous injections for three to thirteen months of small amounts of horse serum. The renal lesions went on to the chronic stage with scarring and atrophy and azotemia.

Inasmuch as a high proportion of antibodies seem to be included in the gamma globulin fraction, the pathogenetic mechanisms of experimental nephritis produced by anti-kidney serums and by the injection of gamma globulins may not be dissimilar. And the possible analogy of these forms of experimental renal disease to human glomerulonephritis, which so characteristically develops with the immune response to an infection, seems highly plausible

These various lines of evidence point strongly to the participation of allergic factors in the pathogenesis of glomerulonephritis. But the actual mechanism by which the allergic response to a streptococcic infection participates in the production of glomerulonephritis still remains an open field for investigation.

Acute Glomerulonephritis as a General Capillary Disease.—In recent years the view has steadily gained ground that acute glomerulonephritis consists not merely in an affection of the glomerular capillaries, but that the glomerular lesions are but one manifestation of a general injury to the capillaries of wide areas of the body. This is really an old theory, for Cohnheim and Lichtheim[160] long ago adduced evidence that edema in postscarlatinal glomerulonephritis is the result of injury to the cutaneous capillaries. Strongly in favor of the theory of acute glomerulonephritis as a general capillary disease is the fact that edema sets in very early in the disease, often almost simultaneously with the proteinuria Indeed, some cases have been described in which edema preceded proteinuria, and even such in which the edema and hypertension were not accompanied by proteinuria at all (see Chapter 20). We have seen in the chapter on Edema that some observations of high protein content of the anasarca fluid in acute glomerulonephritis indicate the presence of injury of the subcutaneous capillaries with resultant increase in permeability These observations, however, have been disputed (p 150)

The direct microscopic studies of the capillaries of the nail bed in acute glomerulonephritis by Weiss,[161] Boas,[162] Hahn,[163] Marriott[112] and others have

led to conflicting results. Weiss found the capillaries to be unusually thick and tortuous and the blood flow slowed. Hahn observed the flow to
Marriott described the capillaries
spastic contraction of the arterial
Boas and Kylin[14] are not inclined
to attribute significance to these findings, for they believe that similar
ondition. But the work
y constriction is present
Kylin claims that the
However, the

spread capillary injury in acute glomerulonephritis should be substantiated, one encounters the further difficulty of explaining why the glomerular capillaries are so much more severely damaged than the others It seems probable that the severe injury to the glomerular capillaries is in some way connected with their excretory function, for even the neighboring intertubular capillaries show as little morphological evidence of damage as those in other organs

Volhard's Hypothesis of the Angiospastic Origin of Acute Glomerulonephritis —

of the absence of blood from these vessels, he believes that the glomerular ischemia is due to a block of the circulation before the terminal portions of the vasa afferentia Not finding organic lesions of these vessels in the early stages, he holds that the circulatory obstruction is functional, consisting in a spasm of the smaller arteries. Volhard regards the glomerular lesions as an expression of the reaction to the resulting ischemia Volhard believes that the arteriolar spasm is not confined to the kidney, but is universal and thereby accounts for the hypertension, the retinal lesions when present, and the pallor of the skin He even accounts for the edema by ischemic injury to the capillaries In favor of this angiospastic theory of acute glomerulonephritis, Volhard and his pupils have adduced the following evidence

Huelse believe that this finding demonstrates that the glomerular ischemia is due to arteriolar spasm which is, of course, relaxed after death and permits the injection of the glomerular capillaries.

2. Huelse and Strauss[163] claim to have demonstrated in the blood of patients with glomerulonephritis and eclampsia gravidarum a substance which sensitizes the arterioles to epinephrine and thereby results in the arteriolar spasm. They originally believed the sensitizing substance to be peptone-like, but then found this improbable, for blood filtrates which they tested gave no biuret reaction.

3. Koch[164] found that the rise in blood pressure may precede the urinary changes of postscarlatinal glomerulonephritis.

Vollhard's hypothesis of primary vascular spasm in acute glomerulonephritis has met with little support apart from an elaborate anatomical investigation by Kuczynski,[122] whose findings do not appear unequivocal and are largely controverted

...

xanr, many of the vasa afferentia contained large numbers of red cells. I have several times made the same observation, as have others. Moreover, the capillary loops are not empty, but, as has been described on page 549, their lumens are narrowed or obliterated by swelling and proliferation of the endothelial cells and other inflammatory exudation. The claim of Huelse and Strauss, that an epinephrine-sensitizing substance is present in the blood in acute glomerulonephritis has never been confirmed and would not prove that the vasoconstriction is the primary factor. And Huelse's finding, that the glomeruli in acute glomerulo-

...

found that the resistance to perfusion of the kidney is increased in acute glomerulonephritis Finally, hypertension only exceptionally precedes urinary abnormalities in postscarlatinal glomerulonephritis It is thus seen that none of the findings on which the angiospastic hypothesis of acute glomerulonephritis is based is unequivocal, and it cannot be accepted as even probable.

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Chapter

20

ACUTE GLOMERULONEPHRITIS. II. CLINICAL PICTURE, DIAGNOSIS, PROGNOSIS, AND TREATMENT

CLINICAL PICTURE OF ACUTE GLOMERULONEPHRITIS

THE clinical picture of acute glomerulonephritis is peculiarly variegated, due not only to the predominance of one or another symptom of the glomerulonephritis itself, but also to the frequent concomitance of other manifestations of the causative infection. In the one instance, the evidence of the disease consists in little more than urinary abonrmalities revealed by routine examination of the urine after scarlet fever or another infectious disease, while in other cases there is an extremely severe clinical picture with marked edema, cardiovascular manifestations, and uremia The disease may run its course in a few days or far more commonly in some weeks, while in other instances it lasts for months or enters a chronic phase; and there are unusual fulminant cases which terminate fatally within a few days or weeks.

Onset.—The onset may be acute or insidious. The following are some of the many ways in which acute glomerulonephritis is first manifested:

1. A *latent* period may constitute the first phase of the disease; during this time, there are no subjective symptoms and the renal mischief is discovered only as a result of routine urinary examination following an infection.

2. *Edema* is very often the initial symptom. Following sore throat or another infectious disease, quickly after exposure to cold or wet, or without any ascertainable cause, the patient notices in the morning that his eye-lids are puffy, or it may be pointed out to him by others. Less commonly, swelling of the feet or genitalia is the first sign

3. *Urinary symptoms* may be noticed first. There is bloody and scanty urine. Occasionally, there are also frequency, urgency and pains in the lumbar region radiating downward, thus simulating disease of the urinary passages.

4. In other instances, particularly following severe sore throat or exposure to cold and wet, the disease sets in with violent *symptoms of an acute infection*, such as high fever, chills, headache and bodily pains, particularly in the back. Vomiting is a common initial manifestation in children. Edema then appears, or in unusual cases it may not come on at all, so that the diagnosis is first suspected from the urinary examination.

5. There are cases, particularly in children, which start with *cerebral symptoms*, such as headache, convulsions, transitory palsies and vomiting.

6. In war nephritis, dyspnea was a common ... been present in 34 of Dunn and MacNee's[1] 51 cases. But it is rarely among the chief initial complaints in glomerulonephritis as seen in civil practice.

7. In children, less often in adults, the onset may be *insidious* with ... loss of appetite, thirst and, perhaps, slight edema, the

... This

tory of

... to Glomerulonephritis.—In the following, some

be

... level as 135/90 mm, which is seen later to be above the normal for the individual. The slight extrarenal manifestations, if present at all, quickly disappear, and then the urinary abnormalities clear up, most often in the course of weeks, but sometimes in a few days. The patient either feels comparatively well or else complains of weakness, lassitude, anorexia, etc., symptoms which may quite as well be after-effects of the primary infection as manifestations of the glomerulonephritis. Such cases represent

the physician for the original sore throat. In all likelihood, such mild

in status epilepticus, and then constitute a grave immediate danger to life. If the patient survives the convulsive seizure, the disease usually pursues its previous course, though in some instances marked amelioration of symptoms follows. I recently saw a middle-aged woman with old

essential hypertension in whom sudden headache, vertigo, vomiting and disorientation led to diagnosis of cerebral hemorrhage or thrombosis; actually, there was acute glomerulonephritis.

A further clinical type of acute glomerulonephritis is constituted by the cases in which *arterial hypertension* and heart failure are the most prominent features, as a rule accompanied by edema, less often by almost none. Cases of this type occur particularly in adults. There are marked dyspnea and other evidence of myocardial insufficiency; sudden failure of the left ventricle with resultant pulmonary edema may occur. This is an unusual form of the disease, and is the one most likely to lead, in adults, to death in the acute stage.

Above were mentioned the cases that start with high fever, chills and other *manifestations of a severe general infection.* This picture usually quickly subsides—though in rare instances death may occur at this time—and the disease then runs the usual afebrile course of glomerulonephritis. These severe general symptoms are probably due to the general infection rather than to the glomerulonephritis and in the rare cases in which the fever stays high for more than a few days, another infectious focus or bacteriemia can generally be demonstrated.

At any period of the clinical course, but particularly at the start, the oliguria which is an almost constant feature of the disease may become intensified so that the patient passes extremely little urine or, rarely, becomes totally anuric. Under these circumstances, retention of urinary constituents occurs and the picture soon becomes that of *uremia* with its characteristic nervous and gastro-intestinal manifestations and its grave outlook. On rare occasions, anuria may alone usher in the disease, as in the following interesting case:

An elderly male was admitted to the Surgical Service of Dr Edwin Beer at Mount Sinai Hospital, his sole complaint being that he had not urinated at all for a week. Otherwise, he felt well. There was marked nitrogen retention but no hypertension or edema. Inasmuch as anuria persisted, decapsulation was carried out two days after admission and a small piece of kidney removed which revealed acute glomerulonephritis. The anuria continued and death from uremia occurred on the fourteenth day; the diagnosis of acute glomerulonephritis was verified at necropsy. From beginning to end, the only symptoms were anuria and, in the last days, the consequent uremic manifestations However, it should be borne in mind that sudden onset of extreme oliguria or anuria is more apt to result from necrotizing nephrosis ("lower nephron nephrosis") than from acute glomerulonephritis

Finally, there are unusual very severe cases characterized by copious *hematuria and rapidly progressive renal insufficiency* from the very start with little edema and no hypertension. Most of the cases of this variety that I have seen died in the acute stage.

The Individual Symptoms.—EDEMA.—Dropsical swelling of the skin is to the laity *the* sign of the disease. It is present in the large majority of patients with glomerulonephritis, but may be absent in the very mild cases and also, on rare occasions, in the most severe It usually appears very early, but may supervene only after the urinary abnormalities have been present for some time. The edema may come on suddenly and rapidly

scale, a stage of so-called pre-... The sudden onset of edema without a protracted stage of pre-... be observed in children whose weight has been followed after sore throat or ... of nephritic edema are

... bed for ... still ... it in ... In ... others it increases rapidly ... extreme general anasarca is rarely seen in acute

... cavities, most often the peritoneum and pleura, which ... paracentesis Further details as to the distribution

It is sometimes preceded by edema of the fauces, and may occur ... as part of generalized edema or alone (Dieulafoy[2]). Since salt restriction has come into use, laryngeal edema is no longer seen in adults Attention has been called to the fact that pulmonary edema is more often due to cardiac failure than directly to the general edematous tendency, and that cerebral edema is probably due to circulatory disturbances in the brain consequent on the hypertension (p. 354). The most extreme general anasarca may be present without any pulmonary or cerebral edema.

The relation of the edema to the other phenomena of the disease is very variable In some mild cases it is entirely absent. It may be very transitory or persist obstinately over months as the disease enters the subacute phase In other instances the edema disappears, despite the fact that the persistence of the hypertension and urinary changes reveal that the disease is still present In some of the most severe cases, there is no edema

the extrarenal capillaries sufficiently to produce edema. In other instances of severe glomerulonephritis, the absence of edema is doubtless due to the fact that the patients ingest no salt and/or vomit.

The edema fluid during the acute stage of glomerulonephritis is clear and not opalescent as is so often seen in the nephrotic edema of the later stages of the disease and of chronic nephrosis. The subcutaneous edema is rarely sufficiently abundant to enable one to obtain an uncontaminated specimen for examination. The pathogenesis and protein content of the edema are discussed on p. 150.

In addition to the renal variety, edema of cardiac origin may occur in acute glomerulonephritis; it is to be recognized by the coexistence of other symptoms and signs of cardiac insufficiency.

Arterial Hypertension.—The classical picture of acute glomerulonephritis includes arterial hypertension. But it is more often absent, or at least not definitely demonstrable, than is edema. Like the latter, it is frequently absent or only transitory in mild cases. In tuberculous and other cachectic patients hypertension is mostly, though not always, slight or absent. In children, hypertension is more apt to be absent than in adults. In the exceptional cases of acute glomerulonephritis in the forties or fifties, hypertension is much more apt to be severe and prolonged than in younger patients. Cardiac failure may at any time reduce the hypertension.

The rise usually affects both the systolic and diastolic pressures. However, the elevation in either may be the more prominent. It is, perhaps, more frequent for the diastolic rise to be proportionately greater. But it is important to bear in mind that there are cases, particularly in children, in which only the systolic pressure is elevated; this is most common at the onset. As a rule, the hypertension is moderate in degree, the most common systolic pressures in adults being between 130 and 170 mm Pressures exceeding 200 mm systolic and 120 mm diastolic occur, especially in older patients, but are unusual in truly acute glomerulonephritis. In some instances, especially in children, blood pressures which cannot be regarded with certainty as abnormally high are seen in retrospect, when the normal value is known, to have constituted slight but definite hypertension for the individual.

While in many cases the arterial tension is consistently elevated, in others it fluctuates greatly. As in essential hypertension, the tendency is for the pressure to be higher toward evening.

The elevation in blood pressure may be found at the very onset of the disease or it may come on gradually, after the edema, hematuria, etc., are well established. It was long ago found by Mahomed[3] and Riegel[4] by means of sphygmographic studies that what they took to be increase in arterial tension may precede the edema and other phenomena of acute glomerulonephritis—the prealbuminuric stage of Mahomed. This has been confirmed by a study of Koch[5] on scarlet fever convalescents He finds that during the period of scarlet fever when glomerulonephritis is most apt to occur, a rise in blood pressure is very common The elevation of blood pressure may or may not be followed by proteinuria and hematuria, and is usually very transient. On the other hand, Steiner[6] found that the changes in the urine in postscarlatinal glomerulonephritis precede the rise

Further investigations to decide the time relations of

The duration of hypertension in acute glomerulonephritis is variable. Most often, it runs parallel to the other phenomena of the disease. But it sometimes drops to normal while the urinary abnormalities and edema are still present or, what is rare but important, the hypertension may outlast all other symptoms but slight proteinuria as the sole strong indication that the patient is not recovering completely, but is entering

manifested by the radial artery remaining palpable in a segment from which the blood has been removed by compression. This phenomenon (pseudo-arteriosclerosis of Moschcowitz) is often readily detectable in

Hypertensive Encephalopathy.—Hypertensive encephalopathy may occur In adults it appears in only a small proportion of the cases; in children the cerebral attacks are more frequent, but even here affect only a decided minority of the totality of patients Since the introduction of salt restriction, full-fledged hypertensive encephalopathy has become a rarity in glomerulonephritis The cerebral attacks occur almost exclusively in patients with arterial hypertension. The elevation of blood pressure is usually great, but in a small proportion of the cases, almost always in children, the hypertension is but moderate

The prodromes and symptomatology of hypertensive encephalopathy have been described in Chapter 11. Here, it may be remarked that the cerebral seizures may come on at any time of the disease while the hypertension is still present, and in very rare instances may even be the initial manifestations of acute glomerulonephritis By far the most common form of hypertensive encephalopathy is severe headache, often accompanied by nausea and vomiting The most striking manifestation is the epileptiform convulsive seizure But other forms, amaurosis, delirium, palsies, etc, occur in rare instances I have found that, in addition to hypertensive headache, slight manifestations—former ... tensive encephalopathy ... nephritis, particularly in ... consist in the most variegated cerebral symptoms—transitory aphasia, weakness of a limb or of one-half the body sometimes accompanied by the Babinski sign, slight ... aroxysmal dyspnea, severe ... een especially interested in ... nomena, which, because of ... by careful questioning and

frequent examination. They can be recognized as manifestations of hypertensive encephalopathy by their association with rises in blood pressure in the absence of any considerable retention of urinary constituents in the blood, and seem to be of little prognostic significance.

Death during a single convulsive seizure is very rare. But there is grave danger if the attacks follow one another rapidly, which is likewise rare under modern treatment. Judging by the older literature, such repeated convulsive seizures were more common at the time when salt was not restricted and fluids were forced. The chief danger during a convulsive seizure is sudden *cardiac failure*. If the episode is survived, it may be followed by distinct improvement in the general course of the disease. The rare anaurosis, transitory palsies, aphasia, etc., clear up rapidly and completely if the patient does not die.

Hypertensive Retinopathy.—The typical picture of hypertensive retinopathy (p. 368) is rare in acute glomerulonephritis and indicates a very severe case with a serious prognosis It occurs only in the presence of severe hypertension. But it was pointed out in Chapter 12 that such cases can recover with complete healing of the retinal lesions, though this is extremely rare. It was also stated (p. 368) that less marked changes in the fundus oculi are not rare in acute glomerulonephritis. With marked hypertension, narrowing of the arterial blood columns may be evident. Dr. H. A. Derow (personal communication) has observed compression of the veins at the arterio-venous crossings, which disappeared with subsidence of the hypertension. Small retinal hemorrhages are not uncommon and seem to be of little significance, they are probably analogous to cutaneous petechiæ.

The Heart.—Goodhart[7] long ago pointed out that cardiac dilatation and failure may develop and even prove fatal in postscarlatinal nephritis. Only in recent years, however, has it been widely realized that heart failure is one of the great dangers in the early days of acute glomerulonephritis. Clinical evidences of cardiac insufficiency were present in one-third of Master's[8] and over two-thirds of Whitehill's[9] patients, and in half the children studied by Lyttle.[10] Burke and Ross[11] found acute glomerulonephritis the most common cause of congestive failure in the Children's Hospital of Washington. In my experience, heart failure has been responsible for the majority of the few deaths in the first days of the disease. It may be precipi[illegible]
Pleural effusion [illegible]
dyspnea. Heart [illegible]
in frequency and severity since salt restriction has been generally practiced.

In the genesis of heart failure in acute glomerulonephritis, two factors are concerned—hypertension and myocardial damage. In most instances hypertension is present and presumably plays a part in producing the cardiac insufficiency. This seems highly probable in the exceptional cases in which a steep rise in pressure is followed by acute left ventricular failure with pulmonary edema.

There are also cases of acute glomerulonephritis in which the heart fails with little or no rise in blood pressure. Here, the factor of myocardial

By taking serial electrocardiograms,

of intraventricular conduction defect, and protraction of the Q-T interval revealing prolongation of electrical systole. Changes in the P-wave may occur Arrhythmias are rare. La Due and Ashman found Wilson's[14] ventricular gradient deviated to the right in 41 and to the left in only 1 of 101 patients, they attribute the right deviation to a combination of hypertension of acute onset and cardiac dilatation. The electrocardiographic changes generally disappear quickly after improvement, but sometimes a negative T_1 persists for weeks.

The cause of myocardial damage in acute glomerulonephritis is not clear. Heart failure and electrocardiographic changes may occur at a stage when there is little or no azotemia or abnormality in the K, Na, Cl or Ca content of the plasma In febrile cases the myocardium may be damaged by toxemia, but this is hypothetical. The muscle fibers are some-

subacute glomerulonephritis. They describe widespread serous effusion between the muscle fibers containing relatively sparse cellular elements; muscle necrosis was rare. The extent to which such interstitial edema participates in the production of heart failure seems problematical.

tricle only after the hypertension had existed for several weeks. Guggenheimer[17] likewise observed in cases of war nephritis that it takes about four or five weeks before left ventricular hypertrophy is found. On the other hand, Friedlander[18] found anatomically that cardiac hypertrophy

weight due to interstitial edema

Moreover, the
often doubtless increased by
sometimes abetted by forming of
measurements with Evans blue, C
first days of the disease

In many cases hypertension does not engender symptoms of cardiac insufficiency, and physical examination of the heart reveals no abnormality. In such patients the pulse is occasionally slow, even down to 50 per minute, but more often bradycardia is not present and there may be tachycardia corresponding to such fever as may exist.

In other patients, with or much less often without hypertension, evidences of a slight degree of cardiac insufficiency make their appearance. These consist in mild or moderate dyspnea and sometimes palpitation or [illegible] an initial symptom. [illegible] light enlargement of [illegible] Relative weakness of the left ventricle may be indicated by the fact that the pulmonic second sound is as loud as or louder than the aortic second sound, despite the presence of hypertension. All of these signs disappear rapidly if the patient improves.

On the other hand, *there are unusual cases in which cardiac insufficiency is very severe and dominates the clinical picture*; death may occur with the typical phenomena of cardiac failure. The heart may give way with startling suddenness, either out of a clear sky or following a convulsion. At the onset the picture is generally that of typical left ventricular failure (see p. 777): There is agonizing dyspnea, orthopnea and cyanosis. The heart rate becomes very rapid, there is gallop rhythm and a functional systolic murmur at the apex and the pulmonic second sound is accentuated; sometimes enlargement to the left can be demonstrated within a relatively short period Moist rales are generally to be heard at the bases of the lungs and at any time outspoken pulmonary edema with its characteristic auscultatory signs and pink, foamy, albuminous expectoration may appear. In some instances the blood pressure falls, in others it rises (see *Hochdruck-stauung*, p. 789). There may be pulsus alternans In those cases which are seen during this stage of predominant left ventricular failure, there is neither peripheral edema nor notable swelling of the liver and the veins are not distended. In some such cases, death from pulmonary edema may be appallingly rapid—the hyperacute asystole of the French. But more often there are added signs of right ventricular failure—enlargement of the liver, distention of the veins with notable rise in venous pressure,* and often cardiac edema—to the consequences of insufficiency of the left heart. In fact, some cases are seen first when signs of failure of both ventricles are present; the right ventricle sometimes gives way close on the heels of the left, with resultant rise in venous pressure and swelling of the liver. But there are also patients in whom the symptomatology for days is that of isolated failure of the left ventircle, the dominant feature being attacks of cardiac asthma (see p 778), with or without demonstrable evidences of pulmonary edema.

* Distention of the veins and rise in venous pressure may not always be indicative of [illegible] engorgement in the absence of signs of left ventricular failure and pulmonary engorgement.

THE l ... urinary findings in acute glomerulonephritis consist ... disease is

The ... evere cases advanc ... It usually anuria ... quickly leads to death, but we mentioned a case ... the anuria lasted fourteen days before the fatal outcome. Oliguria is, as a rule, most marked at the onset and in the first few days when edema is accumulating, but the urinary volume may be small even without edema. The daily output is generally about 400 to 700 cc. The urinary volume usually, but *not always*, diminishes before the onset of convulsions. There are several causes for the oliguria of acute glomerulonephritis:

1 The primary cause is impairment of filtration due to thickening of the walls of the loops and sometimes also to obturation of their lumens. For reasons which remain to be elucidated, the diminution in the volume of filtration is not counterbalanced by an equal decrease in tubular reabsorption of water.

2 If the conception of generalized capillary damage in acute glomerulonephritis is valid, the resultant prerenal deviation may contribute to the oliguria.

3 Cardiac insufficiency may add to the oliguria

4. Vomiting, diarrhea or fever may likewise diminish the urinary volume.

One of the first signs of improvement is generally an increase in urinary volume, which may rise to over 2000 cc. daily as edema is being resorbed

Hematuria —Hematuria is present in almost every case, leading to the name "acute hemorrhagic nephritis." In most instances, there is sufficient b ...

...

cases or at other times the hematuria may be only microscopic. In some very severe cases, there is little blood in the urine, though this is rare. In most instances, marked hematuria is not of long duration, diminishing after a few days or at most weeks. But the microscopic hematuria may be very protracted, a few red cells are often found in the sediment after the proteinuria has cleared up completely, and may last for many months without necessarily indicating that the renal process is becoming chronic. Improvement in the renal condition is sometimes accompanied by temporary increase in hematuria, presumably indicating the reëntry of blood into previously impermeable glomerular loops

Microscopic examination of the sediment shows in addition to well-formed red cells, shadows of cells from which the hemoglobin has been extracted There are often red cell casts There may be also clumps of

...

hemolysis in the arm blood, the hemoglobin must have been freed in the kidneys

The source of the hematuria in acute glomerulonephritis is presumably rupture into the capsular space of glomerular loops which are injured but still permeable.

Proteinuria.—Proteinuria is present in all but extremely rare instances. As a rule, it does not surpass 0.2 to 0.4 per cent, but in unusual cases it may exceed even 2 per cent. The amount of protein does not necessarily run parallel to the severity of the case. The proteinuria usually outlasts the other notable phenomena of the disease, though often microscopic hematuria is present long after the protein reactions become negative. During convalescence, the proteinuria sometimes becomes distinctly orthostatic in type, appearing only when the patient leaves the bed and the urinary volume falls as a result of decreased renal blood flow (p. 122). This may last for months. The acetic acid body may be present long after the urine no longer clouds on boiling.

A small number of cases of acute glomerulonephritis have been published in which proteinuria was absent either entirely or for a considerable time

[illegible]

in which proteinuria was either absent or but intermittently present; in 2 of the cases, the diagnosis was verified at necropsy. The same was observed by Nonnenbruch[21] and Guggenheimer[17] in war nephritis. Wickbom[22] also studied 3 cases with an acute clinical picture characterized by hypertension, edema, hematuria, and cylindruria, in which proteinuria was either absent or intermittent. Following a sore throat, a sixteen-year-old girl studied by Crofton and Truelove[23] developed edema and a blood pressure of 182/110 mm.; no urinary abnormality was detected except proteinuria on the eleventh day. Among 248 cases of acute nephritis, Allesandri and Rosihman[24] observed 6 without or with only minimal urinary changes, in 1 of these, necropsy revealed acute glomerulonephritis.

The Urinary Sediment.—The urine almost always deposits a heavy sediment, usually brownish-red in color. With severe hematuria, it may be bright red. In addition to numerous red cells and frequently large quantities of urates, the sediment contains the following elements:

Casts are practically always present. In the earliest stage, hyaline and blood casts are usually the only varieties found, but later granular, epithelial, sometimes fatty and rarely waxy casts appear Casts containing doubly refractile lipoids are not found in the first period, their presence speaking for a considerable duration of the process with marked secondary tubular lesions

Cylindroids are generally also present and may be particularly abundant during convalescence, as the last urinary sign of the disease (Lichtwitz[25]).

Leukocytes almost always occur in numbers greater than that corresponding to the blood present; they are, as a rule, particularly numerous in the first period

Epithelial cells are usually few in number or absent at first; later, with the onset of tubular degeneration, they appear in large numbers

Specific Gravity of the Urine.—When renal function is little impaired, the specific gravity of the urine is high (1022 to 1032) because there is prerenal deviation of water into the tissues to form edema and the density

[illegible] mixture of blood and protein. In such urine, the [illegible] for the [illegible] The [illegible]

specific gravity is [illegible]

[illegible] mixture of blood or massive [illegible]

varies greatly From the clinical point of view, [illegible] may be differentiated: they often follow one another as successive stages in the evolution of the disease:

1. *Relatively Intact Renal Function* —There may be little impairment of renal function, the patient can form both a highly concentrated and very dilute urine, the urea clearance is tolerable, and there is no nitrogen retention in the blood. This may occur at the start, and it may persist throughout the course of cases the diagnosis of which is definitely established

[illegible] the former is due to decrease in glomerular filtration and the latter affords evidence that the concentrating ability of the tubules is little impaired. The diminution in glomerular filtration has been demonstrated by measurements of inulin clearance (p 578). The oliguria may be so marked that, despite the high concentration of the urine, there is pronounced nitrogen retention The nitrogen retention may have the characteristic that the urea is greatly elevated while there is little change in the creatinin. This is presumably due to urea being eliminated solely by glomerular filtration while creatinin is excreted not only by glomerular filtration but also by tubular secretion Since tubular function is good, the creatinin content

greatly obstructing blood flow through the loops so that the blood supply to the tubules remains fairly adequate Isolated impairment of glomerular filtration in acute glomerulonephritis may be very transient or last even as much as two weeks; it is succeeded either by improvement or by the addition of impairment of tubular function.

3. *Combined Impairment of Glomerular Filtration and of Tubular Function.*—Clinically, damage to tubular function is revealed by hyposthenuria. Presumably, at this stage the glomerular lesion is such that it not only hampers filtration but also impedes blood flow through the glomeruli to such an extent that the blood supply to the tubules is inadequate.

For the impairment of renal function to lead to death from true uremia during the acute stage is decidedly unusual; many of the cases that are considered as such are really instances of hypertensive encephalopathy or cardiac failure. Uremia occurred in but 19 of Barasch's[26] 232 cases of postscarlatinal glomerulonephritis, and in this number are included some instances of hypertensive encephalopathy. When uremia does supervene, it presents the same picture as when due to other causes—nausea, vomiting, apathy deepening to stupor and then to coma, muscular twitchings, etc.

INDIVIDUAL RENAL FUNCTIONS.—In recent years, a number of measurements of the discrete renal functions have been carried out in acute glomerulonephritis, though unfortunately few in the first days of the disease. These have revealed depression in glomerular filtration greater than in renal blood flow and in such tubular functions as have been measured.

Measurements of *renal blood flow* by the diodrast or PAH clearance (Earle[27] *et al.* and others) have most often revealed a decrease, in some instances to very low levels. However, observations by Earle,[27] Bradley[28] and others show that some patients pass through a stage of renal hyperemia with increased blood flow; Bradley's observations may be accepted as unequivocal, inasmuch as he corrected the PAH clearance by the PAH extraction obtained by catheterization of the renal vein.

Glomerular filtration (inulin or mannitol clearance) is subnormal in the large majority of instances The depression in glomerular filtration is greater than in renal plasma flow, with the result that the *filtration fraction* is below normal. Greater diminution in glomerular filtration than in renal blood flow would be anticipated to result from lesions which start in the walls of the glomerular loops

Observations with regard to *tubular functions* have varied, probably largely in accord with the stage of the disease Bradley found subnormal extraction and maximal tubular excretion of PAH, revealing functional impairment of the tubules. Contrariwise, in 1 case of acute and 3 of subacute glomerulonephritis, Cargill[29] observed PAH extraction within normal limits. In Earle's observations, maximum excretion of PAH was unaffected in mild cases and, when depressed, was less so than glomerular filtration. Earle *et al.* found that glucose reabsorption is relatively little affected in acute glomerulonephritis, and that ammonia excretion is not decreased in the early stages of the disease although it becomes so later. As stated above, the clinical and anatomical findings indicate strongly that patients with acute glomerulonephritis pass at the onset through a stage in which glomerular filtration is diminished while tubular functions are still intact It would be desirable to have this conception fortified by measurements of the individual functions in the *first* days of the disease.

Low *oxygen consumption* of the kidney, despite normal renal blood flow, was found in glomerulonephritis by Cargill and Hickam[30] However, none of their cases was of less than five weeks duration.

BLOOD CHEMISTRY.—The chemical changes in the blood in renal insufficiency resulting from acute glomerulonephritis do not differ from those in other varieties of renal failure, except for the above mentioned instances in which the urea content of the blood rises in the absence of creatinin retention. Because of the usually brief duration of impairment of renal function, the fact that the patients are kept on a restricted diet, and the formation of edema which stores urinary constituents in about the same concentration as the blood, it is unusual for high degrees of retention to develop. But in some instances this does occur. With anuria, *of course*, maximal retention develops.

The concentrations of sodium and of chloride in the blood vary greatly. De Wesselow[31] long ago observed that the serum chloride level may be either elevated or depressed. There are a number of factors influencing the sodium and chloride concentration. Impaired renal function and the ingestion of salt by patients whose diet has not been properly restricted elevate the sodium and chloride The absorption of edema (which has a higher chloride content than the blood) tend to raise the chloride of the blood.

same patients Hyperpotassemia is rare in acute glomerulonephritis and

omiting and

ences. The

ting tend to concentrate the blood, while impairment of glomerular filtration, ingestion of water and absorption of edema tend to dilute it and

plasma volume that in acute and subacute glomerulonephritis with edema the *plasma* volume averages within normal limits (51 9 cc per kilogram body weight) though there

red cell volume, though here also some cases were normal. Lichtwitz[33] observed increased blood volume in several cases of very early glomerulonephritis Litzner[34] also found the blood volume increased in acute glomerulonephritis when hypertension was present. Nonnenbruch[35] observed that while in most edematous nephritics the blood is either normally concentrated or hydremic

entration is

s, Cardozo[36]

were low and returned to normal in a fortnight. With Evans blue, he found that the plasma volume

days than later

nephritis with sev

hydremia, but th in the course of the disease opposing influences may decrease or increase the blood volume.

The total protein content of the plasma is within normal limits in the early stages of acute glomerulonephritis. Examination of the individual protein fractions usually reveals the albumin and globulin to be approximately normal in the initial stages, but sometimes there is increase in globulins and in fibrinogen (Starlinger[37]); the latter is doubtless to be regarded as a manifestation of the infection. The normal concentration of plasma albumin shows that edema in acute glomerulonephritis is not due to diminished colloid osmotic pressure of the plasma as in chronic nephrosis and often in subacute and chronic glomerulonephritis. It usually takes at least several days of loss of large quantities of albumin in the urine to diminish plasma albumin notably.

The blood cholesterol and other lipids are likewise normal in acute glomerulonephritis, in contrast to the later stages and chronic nephrosis.

The Blood Cells.—Despite the pallor of the patients, there is no anemia in the very first stages, unless it is present as a result of the primary infection. Later on, secondary anemia generally develops and may become very severe (Chapter 21). Nor is the white cell count always influenced by the renal process, though there is often moderate polymorphonuclear leukocytosis when the onset is febrile. The sedimentation rate of the red blood cells is usually accelerated.

The Lungs.—Diffuse bronchitis causing annoying cough is not uncommon. In many fatal cases of war nephritis, Dunn and MacNee[1] found focal pulmonary lesions of peculiar histology, which they considered as frequently responsible for severe dyspnea The latter is, however, most often due to left ventricular failure. Pneumonia was formerly a fairly common complication, particularly in children. Pospischil[38] found it in 11 per cent of his cases of postscarlatinal glomerulonephritis. Since penicillin, pneumonia is rare. The occurrence of pulmonary edema as a result of cardiac failure was mentioned above.

Gastro-intestinal Symptoms.—Nausea, vomiting and either diarrhea or constipation are common at the onset in children They may also occur, though less often, when there is a very abrupt onset in adults, and and yet not be a manifestation of uremia. In such non-uremic cases, the vomiting may, perhaps, be interpreted as reflex from the acutely swollen kidney, akin to the reflex vomiting in nephrolithiasis Or it may be due to hypertensive encephalopathy. Nevertheless, during the course of acute glomerulonephritis, vomiting should always raise the suspicion of uremia.

The Skin.—The patients are usually, though not always, pale The pallor is not entirely due to anemia, for it occurs in patients with normal amounts of hemoglobin. Volhard[39] considers the pallor a manifestation of the universal vasoconstriction which causes the hypertension, but this is probably not the whole story for it also occurs in chronic nephrosis, where there is no reason to believe that vasoconstriction is present Quite probably, slight degrees of edema contribute to the pallor by increasing the opacity of the skin. During the formation and persistence of the edema, the skin is often preternaturally dry. It has been found that at this time the insensible perspiration is diminished, and it is difficult to make the patients sweat by diaphoretic measures.

OTHER S[illegible] degree may be present, particularly at the [illegible] Quite proba[illegible] than to the renal process, [illegible] afebrile course. Postscarlatinal [illegible] 102° F. or more during the first few days, though the [illegible] Even here, it is doubtful [illegible] disorder in [illegible] sickness," such as sore throat, lymphadenitis, etc. Convulsive [illegible] generally accompanied by fever. In adults, most cases are completely afebrile after the first few days or during the entire course, unless pneu- [illegible]

[illegible] by tenderness [illegible] been thought by some to be due to stretching of the renal capsule by the swollen kidney. Bradley[39] has suggested that the hyperemia he demonstrated in some [illegible] possible explana[illegible] of the capsule, the actual [illegible] necropsy and during decapsulation operations

Urgency and frequency with the painful passage of small quantities of urine are likewise not uncommon early complaints The explanation of these symptoms is also not clear, they may, perhaps, be connected with the congestion of the mucous membrane of the urinary passages that is occasionally seen at necropsy Nocturia is very common.

In very rare cases, the *spleen* is sufficiently enlarged to be palpable. This was not so rare in war nephritis The splenomegaly is presumably [illegible] be concerned

Occasionally, *purpuric spots* appear in small numbers. While thrombopenia is often present (see Pakozdy[40]), it is rarely marked. With improvement, the platelets rise to even above the normal, accompanied by an [illegible]

Epistaxis is not infrequent, capillary injury, thrombopenia and hypertension are factors that may be concerned in producing the nosebleeds.

DIAGNOSIS OF ACUTE GLOMERULONEPHRITIS

The diagnosis presents no difficulty in the typical case in which the urinary abnormalities are accompanied by edema or hypertension, or both.

But even under such circumstances, the prognostically important question may arise whether the present illness is truly acute glomerulonephritis or an acute exacerbation of a chronic process. The presence of well-marked [illegible] f myocardial insuf- [illegible], for when the heart is notably enlarged in acute glomerulonephritis there is usually also other evidence of cardiac failure. On the other hand, cardiac hypertrophy or dilatation is not demonstrable by physical or radiographic examination in many cases of chronic glomerulonephritis, particularly in the nephrotic type of the disease. Very great hypertension, above 200 mm. systolic pressure, speaks in favor of an old renal lesion, though this is by no means unequivocal, for such pressures are occasionally observed in acute glomerulonephritis. Of course, lower pressures occur in both the acute and the chronic stage. The presence of sclerotic peripheral or retinal arteries also argues for a process of long standing, though here the occurrence of spasms of the arterial wall in acute cases must not be forgotten. None of the criteria are absolute, and in some cases the differentiation between acute glomerulonephritis and an acute exacerbation of a chronic process is impossible; where the clinical evidence seems to speak strongly in favor of the former, chronically diseased kidneys may be found at necropsy.

When microscopic or macroscopic hematuria appears during an acute infection, such as tonsillitis, erysipelas, pneumonia, osteomyelitis, etc., the differentiation between acute glomerulonephritis and focal nephritis arises. The presence of edema, hypertension or impairment of renal function speaks immediately for glomerulonephritis. If the urinary findings appear several days or more after a sore throat has subsided, they are more likely to be the result of true glomerulonephritis, but during the height of the infection either may arise. It should be remembered that it is extremely rare for glomerulonephritis to appear in the course of infections other than streptococcal. In general, therefore, it is wise to consider hematuria in infections due to bacteria other than streptococci or viruses as not due to diffuse glomerulonephritis, unless proved to be so by the appearance of nephritic edema or hypertension—an exceedingly rare event.

In subacute bacterial endocarditis, hematuria may be due to gross infarction, multiple glomerular thrombosis or diffuse glomerulonephritis. The presence of nephritic edema or hypertension is evidence for diffuse glomerulonephritis, though their absence does not speak against it In fact, in the vast majority of instances of diffuse glomerulonephritis complicating subacute bacterial endocarditis, there is neither hypertension nor edema. Impairment of renal function is also very strong evidence in favor of diffuse glomerulonephritis, for it is excessively rare in multiple glomerular thrombosis.

Acute glomerulonephritis may also be confused with periarteritis nodosa involving the kidney. The differentiation depends on the presence or absence of the positive criteria of arterial disease in other organs, marked eosinophilia is present in some, though not all, cases of periarteritis nodosa, but is absent in glomerulonephritis. It should be remembered that periarteritis implicating the renal arteries may produce hypertension. The

borne in mind; hypertension is rare in ...

PROGNOSIS OF ACUTE GLOMERULONEPHRITIS

The outlook in acute ... nephritis is, in general, comparatively good for a disease which ... the three outcomes—complete ... acute stage—recovery is more common than chronicity, while death during the acute stage is exceptional. Of children, the large majority recover completely, while with increasing age at the time of onset the proportion that become chronic rises greatly.

Post... to six weeks. However ... slight ... uria persists for several months. The longer the proteinuria ... the greater the chance of a chronic, irreversible process developing, but complete recovery may occur after a year and even, in rare instances, ...

Caiger[22] observed only 2 cases of proteinuria of more than six ... duration in 65 cases of scarlatinal nephritis that had developed in the hospital and 3 chronic proteinurias among 12 patients who were admitted already suffering from scarlatinal nephritis. Hansberg[43] found that of 284 persons who had had scarlatinal nephritis from one to ten years before the examination, only 1 had proteinuria of five years' duration. Rosenfeld and Rechenstamm[44] examined 92 individuals who had had scarlatinal nephritis from six to ten years previously, and of whom 52 still had protein-...

In the unusual cases that become chronic, the typical picture of chronic glomerulonephritis develops. It may terminate fatally within months or years. I have seen cases in which proteinuria has persisted for forty years.

Death during the acute stage of postscarlatinal glomerulonephritis occurs in a small proportion of cases. Barasch[26] observed 14 deaths in

But even under such circumstances, the prognostically important question may arise whether the present illness is truly acute glomerulonephritis or an acute exacerbation of a chronic process. The presence of well-marked [illegible] uptoms of myocardial insuf- [illegible] glomerulonephritis, for when the heart is notably enlarged in acute glomerulonephritis there is usually also other evidence of cardiac failure. On the other hand, cardiac hypertrophy or dilatation [illegible] many case[illegible] of the disease. Very great hypertension, above 200 mm. systolic pressure, speaks in favor of an old renal lesion, though this is by no means unequivocal, for such pressures are occasionally observed in acute glomerulonephritis. Of course, lower pressures occur in both the acute and the chronic stage. The presence of sclerotic peripheral or retinal arteries also argues for a process of long standing, though here the occurrence of spasms of the arterial wall in acute cases must not be forgotten. None of the criteria are absolute, and in some cases the differentiation between acute glomerulonephritis and an acute exacerbation of a chronic process is impossible; where the clinical evidence seems to speak strongly in favor of the former, chronically diseased kidneys may be found at necropsy.

When microscopic or macroscopic hematuria appears during an acute infection, such as tonsillitis, erysipelas, pneumonia, osteomyelitis, etc., the differentiation between acute glomerulonephritis and focal nephritis arises. The presence of edema, hypertension or impairment of renal function speaks immediately for glomerulonephritis If the urinary findings appear several days or more after a sore throat has subsided, they are more likely to be the result of true glomerulonephritis, but during the height of the infection either may arise. It should be remembered that it is extremely rare for glomerulonephritis to appear in the course of infections other than streptococcal. In general, therefore, it is wise to consider hematuria in infections due to bacteria other than streptococci or viruses as not due to diffuse glomerulonephritis, unless proved to be so by the appearance of nephritic edema or hypertension—an exceedingly rare event.

In subacute bacterial endocarditis, hematuria may be due to gross infarction, multiple glomerular thrombosis or diffuse glomerulonephritis The presence of nephritic edema or hypertension is evidence for diffuse glomerulonephritis, though their absence does not speak against it. In fact, in the vast majority of instances of diffuse glomerulonephritis complicating subacute bacterial endocarditis, there is neither hypertension nor edema. Impairment of renal function is also very strong evidence in favor of diffuse glomerulonephritis, for it is excessively rare in multiple glomerular thrombosis

Acute glomerulonephritis may also be confused with periarteritis nodosa involving the kidney. The differentiation depends on the presence or absence of the positive criteria of arterial disease in other organs; marked eosinophilia is present in some, though not all, cases of periarteritis nodosa, but is absent in glomerulonephritis. It should be remembered that periarteritis implicating the renal arteries may produce hypertension. The

Acute glomerulonephritis complicating *purpura* seems to be a particularly dangerous variety, for of Osler's[69] 14 collected cases, 5 ultimately died of uremia.

. . . hritis supervenes in *subacute bacterial endo-*

disease

The chief *sources of danger* in acute glomerulonephritis are acute myocardial insufficiency resulting in pulmonary edema, uremia, and hypertensive encephalopathy. Extreme oliguria is always a danger signal, foreboding uremia if not relieved. Sometimes diminution in the volume of urine precedes hypertensive encephalopathy. Complete anuria for any considerable length of time is almost always fatal, though patients have . . . known to recover after two days of anuria. I saw one who did so

terminate fatally In former times, edema of the larynx was apparently not uncommon as a cause of death, but is scarcely seen nowadays since salt restriction has been introduced Pneumonia and other infections were

a few weeks or months It has seemed to me that the chances of chronicity are less in those patients who have profuse hematuria but relatively little proteinuria than in those in whom hematuria quickly subsides and is fol-

very high, the case is undoubtedly severe and the outlook is always in doubt until the pressure comes down Persistence of hypertension indicates a process that is very likely to become chronic It should be borne in mind, however, that in rare cases which rapidly die of uremia, there is

teinuria is often orthostatic, the appearance of a definitely cyclic proteinuria, in my observations, has presaged complete recovery. Rubin[61] and his associates found in children that while the routine urinalysis became

much the same in the different etiological varieties of acute glomerulonephritis.

Acute glomerulonephritis following tonsillitis and other infections of the respiratory tract also terminates in recovery in most instances, but in these patients the incidence of chronic renal disease is higher than after scarlet fever. Possibly, particularly after throat infections, the reason is that an infectious focus may persist and continue to injure the kidney, but this expl ... cases (p. 601). In adults the frequency of a ... eater than in childhood, but it must be consi ... attacks in older people may in reality be recrudescences. Death during the acute stage is more likely to occur in children than in adults. Thus, Clausen[47] had 21 deaths in 102 cases of acute glomerulonephritis in children, of which 26 were postscarlatinal. Of the 21 deaths, 10 were from uremia, (presumably including hypertensive encepholopathy), 4 pneumonia, 2 cardiac failure and 1 whooping cough. Of 38 cases of acute glomerulonephritis in children followed for a year or longer by Lyttle and Rosenberg,[48] 30 were cured, 4 became chronic and 4 died; of the 4 deaths, 2 were due to uremia, 1 each to sepsis and pneumonia ... by Kohn,[49] 5 per cent ... from one to twenty years, 85 per cent recovered completely, 5 per cent developed progressive chronic glomerulonephritis and the other 10 per cent renal disease with proteinuria that did not progress within the period of observation. Burke and Ross[50] studied 90 children with acute glomerulonephritis; 64 recovered completely, 3 died of heart failure, and 3 developed chronic renal disease. Most of the few deaths in children that I have seen during the first days of the disease have likewise been of heart failure. Lyttle[10] reported a mortality rate of 9.4 per cent in 722 cases of acute nephritis in children observed by different clinicians.

My experience in adults with definite glomerulonephritis has been that hardly more than half the patients recover completely. Longcope[51] found that only 42.5 per cent of 134 patients with acute glomerulonephritis recovered completely. Similar observations were made by Murphy and Peters.[52] Only a small proportion succumb during the acute stage, while the others remain with at least proteinuria to show that the kidneys have not healed completely.

In *trench nephritis* the mortality during the acute stage was low. Maclean[53] had 4 deaths in 500 cases, Keith and Thomson[54] 2 3 per cent mortality in 300 cases, and Toeniessen[55] 3 per cent in 254 cases. However, a considerable proportion of the patients developed chronic glomerulonephritis Thus, Hume and Nattrass[56] studied 281 men who suffered from "acute nephritis" during the World War. They found that while 45.5 per cent show no evidence of renal disease, 9 5 per cent have advanced chronic nephritis and 2.5 per cent have died of the disease. "The remaining 45 per cent show evidence of some permanent damage to the kidney and are probably developing the disease." Almost identical observations were made by Gros,[57] only 44.6 per cent of whose patients with war nephritis recovered completely. During World War II, Brod[58] likewise observed a high incidence of chronicity.

extensive investigations of Pospischill and Weiss,[38] who fed one-half of 2,373 scarlet fever patients with a milk diet while the other half got the usual meat ration The incidence of glomerulonephritis was almost the same in both groups, but the general medical and physical state of the children who were given meat was far the better. Identical results were ... 1000 scarlet fever patients. Dietary restriction,

full diet including ...
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General Management. —
acute stage of the disease,
Apart from the fact that leaving bed may entail exposure to cold, the
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for the following three reasons:

1 There is no doubt that cold is an important predisposing factor in the causation of the underlying infection in many cases of *glomerulonephritis.*

2. There is experimental evidence that the vessels of the kidney react consensually with those of the skin, and in view of the intense ischemia of the glomeruli so characteristic of acute glomerulonephritis, it would seem that the renal vasodilatation that apparently accompanies cutaneous vasodilatation is much to be desired. However, it remains to be proved that the vessels of the diseased kidney react as they do in experiments on healthy animals

3. The increased elimination through a warm skin relieves the kidney of a certain amount of work, though this is not quantitatively very significant

Sweating procedures were formerly popular in the treatment of acute glomerulonephritis, but have lost much of their vogue in recent years. In the chapters on Edema and Uremia, it was seen that the quantities of

diaphoresis in acute glomerulonephritis. The same is true of vigorous massage, which was formerly also used, Ekgren[40] has observed that the latter may augment proteinuria.

The bowels should, of course, be kept open and best somewhat loose, but the vigorous purgation so popular in former days is *to be avoided.* Mercurial cathartics should not be used because of their nephrotoxic potentialities to ischemic kidneys Magnesium sulphate should be avoided with marked azotemia (p. 66).

TREATMENT OF ACUTE GLOMERULONEPHRITIS

The treatment of acute glomerulonephritis is largely symptomatic, for we have no means at our disposal to influence favorably the course of the lesions in the glomeruli and we are usually unable to influence the disease through combatting specifically the primary infection. The high hopes entertained that sulfonamides and penicillin would accomplish the latter and cortisone or ACTH the former have not been fulfilled. Nevertheless, the increase in knowledge of the nature, and especially the pathological physiology, of acute glomerulonephritis in recent years has entailed more rational therapy, particularly dietetic. While the opinion expressed repeatedly by Volhard,[63] that no patient should die directly of acute glomerulonephritis, is much more optimistic than justified by my personal experience, there is no doubt that a great deal can be done for the patient by careful attention to the details of treatment and the avoidance of all schematicism.

PROPHYLAXIS.—Data do not seem to be available to decide whether treatment of tonsillitis and other infections with antibiotics lessens the incidence of glomerulonephritis. The point could be settled by treatment with antibiotics of alternate members of a large series of comparable infections, but such a series has not been published. Many cases of acute glomerulonephritis are seen in which the causative sore throat was treated with adequate amounts of penicillin. Glomerulonephritis seems to the writer to have greatly diminished in frequency in New York City in the past twenty years and is more common in the economically unfortunate groups; but whether these differences are due to sulfonamides and penicillin or to a lesser incidence of causative infections remains to be decided.

The important role in the etiology of acute glomerulonephritis played by infections of the lymphatic ring in the throat was indicated above. The removal of *definitely diseased* tonsils and adenoids may, therefore, serve to prevent some cases of acute glomerulonephritis This, of course, does not mean the ruthless and wholesale removal of every tonsil large enough to be seen, as is so commonly practiced, but only those in which the evidence of infection seems clear-cut. Unfortunately, however, the experience with glomerulonephritis is precisely that with rheumatic fever; unabated progression is often seen despite technically adequate removal of the tonsils, and many initial attacks are encountered where the tonsils have been removed completely years before. Truly diseased teeth should likewise be removed, but here also the unnecessary zeal of recent years should be avoided; the same applies to the paranasal sinuses, which are operated upon far too often.

Osman[64] found that the administration of antiscarlatinal serum to patients with scarlet fever is of no value in the prevention of nephritis. After the febrile period, the convalescent should be carefully protected from cold and respiratory infections for a period of four weeks. In fact, some authorities keep convalescents from scarlatina in bed for this period, but there is no evidence that this helps to prevent renal complication. In the past, great stress has been laid on the value of a milk diet as a prophylactic of postscarlatinal glomerulonephritis. This belief was shattered by the

3 Carbo[illegible] ...ent to carbon dioxide and water, of which the fo[illegible] any work. to keep the [illegible] little or no protein is included in the diet. Carbohydrate [illegible] ...ents of the diet in the first days of acute [illegible]

and fat intake [illegible] interfere with this objective and it may then be necessary to give [illegible] or fructose by infusion.

4. The water intake must be regulated in accord *with the output.* During the period of severe oliguria that usually initiates acute glomerulonephritis, there is no use in giving large quantities of fluid, for it is not excreted and produces edema and hydremia. The fluid intake *should* [illegible] ...volume plus the extrarenal loss of water. This is gener- [illegible]

Volhard[63] went even further in the principle of saving the kidney from work. He initiated the treatment of acute glomerulonephritis by practically co[illegible] days [illegible] He belie[illegible] it rests the kidney as completely as possible, prevents increase of edema, tends to lower blood pressure and avert convulsive seizures, and diminishes any hydremia that may be present, thereby sparing the heart. Volhard found that patients bear the hunger and thirst very well. For the first few days there is even little complaint of thirst. Lichtwitz[64] also has seen no ill-effects from this seemingly very rigorous procedure, and believes it to be the ideal treatment of acute glomerulonephritis. Volhard continued the starvation and thirst until diuresis, diminution in edema and other evidences of improvement set in, up to a maximum of about five days (Lichtwitz has used the procedure for even a week), and then puts the patient on a progressively more liberal diet regulated in accord with the principles outlined above

I have *observed* excellent results from Volhard's method of almost absolute starvation and thirst in acute glomerulonephritis However, there was no evidence that these results were superior to those obtained by following the principles detailed above. Many of the patients complained of thirst after a day or two and evidences of dehydration were not rare. Moreover, it appeared that weakness was more apt to be pronounced than with a more adequate caloric intake. Theoretically, there are objections

happier than those kept on Volhard's thirst and starvation regimen and the renal process appears to do quite as well. The starvation treatment probably helps almost entirely through the effects of maximal sodium

Dietary Treatment.—The regulation of the diet forms the cornerstone of the treatment of acute glomerulonephritis. In recent years there has been, in many respects, a complete reversal of the principles formerly followed in the dietotherapy of the disease. In the days when it was believed that obturation of the renal tubules by casts and detritus causes the *oliguria*, it was customary to give large quantities of fluid in an effort to increase the diuresis and "flush out the kidneys." For this purpose, milk was used, as much as 3000 or 4000 cc. being given daily. But it has been pointed out that this "flushing-out" treatment usually does not fulfil its purpose in acute glomerulonephritis. The urinary volume is not increased, and the large amount of fluid ingested serves only to increase the edema and sometimes to produce hydremia that increases the work of the heart. That such hydremia actually occurs is shown by the observation of Siebeck,[47] that when large amounts of fluid are given to such patients, there is abnormally great and protracted dilution of the blood. It was during the popularity of treatment with large amounts of fluid that enormous degrees of edema were seen, a manifestation that rarely occurs in a properly managed case of acute glomerulonephritis.

The use of large quantities of milk in acute glomerulonephritis seems ill-advised from at least four standpoints:

1. As just mentioned, if the urinary volume is not correspondingly increased—and in the acute stage it generally is not—edema increases and transitory hydremia may be produced with resultant elevation of the cardiac load.

2. Three liters of milk contain almost 5 grams of sodium chloride, which aids in the retention of fluid.

3 Milk is rich in protein (30 grams per liter), a very strong objection in a disease in which renal insufficiency may supervene at any time.

4. In acute glomerulonephritis, the glomerular loops are largely blocked (page 549), and the blood does not flow through them. It is difficult to see how ingestion of fluid can cause diuresis from glomeruli whose capillaries are impermeable to blood

For these reasons, the ingestion of large quantities of milk or other fluids in the early stages of glomerulonephritis seems irrational, and is undoubtedly a method of treatment that has done great harm in the past.

The diet in acute glomerulonephritis should be that which makes as little call as possible on the excretory and homeostatic functions of the kidney The diet will minimize (1) retention of potential urinary constituents and (2) alterations in the composition of the extracellular fluid consequent on intake of food which are kept small by normally functioning kidneys but are augmented when these organs are diseased. It may also be thought that lessening the work of the kidney favors

Such a diet may be devised in accord wit

1. Protein should be restricted at the ‹ products are almost entirely excreted by the kidneys. In the first week of the disease the patient does not have hypoproteinemia. If after this plasma protein deficit develops, the protein content of the diet must be increased.

2. Sodium chloride is likewise excreted almost altogether by the kidneys. The hydropigenic action of sodium is a fundamental disadvantage. The diet should, therefore, be salt poor.

a result of vomiting, sodium chloride infusions are to be avoided because of the tendency to edema and hypertension. During the intravenous i ion the patient is to be watched carefully for evidences of cardiac ... or pulmonary edema. If

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tension, one should be especially cautious ... the intravenous route. *If there is heart failure, intravenous infusion is contraindicated* because of the great danger of pulmonary edema. I have witnessed the precipitation of pulmonary edema during intravenous infusion in acute glomerulonephritis. It has seemed to the writer that intravenous infusions are used more often than necessary in recent years in acute glomerulonephritis. If the patient can take the fluid by mouth, l ll for the intravenous route.

treatment of anemia

Sulfonamides and Antibiotics.—When sulfonamides and penicillin were

nephritis. While Moncrieff[69] and Suchecki[70] reported soon after the introduction of penicillin that this antibiotic is of value in acute glomerulonephritis, the early hopes have not been fulfilled. There seems to be no

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biotic. This appears to be true even in those cases in which the causative sore throat is still definitely an active streptococcic infection which is cleared up by penicillin. Nor have I seen any beneficial effect on glomerulonephritis from aureomycin, *chloromycetin or terramycin.* Rapoport[71] *et al.* found no significant differences in the course of acute glomerulonephritis between 33 patients treated with sulfonamides and 40 controls who did not get these drugs. Penicillin or another antibiotic should be used for the treatment of infection present in a patient with acute glomerulonephritis, but not with the expectation of influencing the renal lesion. The above-mentioned antibiotics should perhaps be given preference to even highly soluble sulfonamides for fear of nephrotoxic action in an already diseased kidney, although the writer has not seen renal damage due to sulfonamides in acute glomerulonephritis. It should be remembered that with hyposthenuria, while the danger of crystallization of sulfonamides in the tubules is eliminated, high blood levels are quickly attained and persist (*cf.* Fishberg)[72].

restriction on edema, hypertension and heart failure, and these can be obtained quite as well with a salt-poor diet containing considerable quantities of carbohydrate and fat. I have therefore abandoned the starvation regimen except for a day or two in rare cases with pulmonary edema or repeated convulsions due to hypertensive encephalopathy.

The general plan of treatment may be as follows in a case of acute glomerulonephritis starting with marked oliguria and seen at the onset: For the first three or four days, the daily fluid intake is about 1100 cc. more than the previous day's urinary volume (plus allowance for vomiting, diarrhea and fever), no salt is allowed, and the patient is given liberal quantities of carbohydrates and fats. Among the foods that may be used are fruit, sugar, honey, jellies, rice, salt-poor prepared cereals (Cream of Wheat, Farina, etc.), potato, tapioca, cornstarch, protein-poor vegetables, butter, cream and olive oil; and such fluids as fruit juice, coffee, tea, ginger ale and other sweet drinks to the limit of the fluid allowance. After the first few days, unless there is azotemia, enough protein to maintain nitrogen balance (page 226) is added in the form of salt-poor bread, meat and eggs. Dialyzed milk may be useful, but is dear. If there is nitrogen retention, protein restriction is continued. In the presence of extreme oliguria or anuria, the considerable potassium content of vegetables and of orange and grapefruit juices should be borne in mind.

As the patient improves, the diet is made more and more liberal, but until the urine has become normal the protein should not greatly exceed the amount necessary to maintain nitrogen equilibrium and the salt intake should be restricted to about 5 grams daily. After the hypertension and edema have vanished and the protein and formed elements have disappeared from the urine, I can see no object in prolonging dietary restriction. Nor can I see any advantage in restricting the diet of those patients who have recovered completely except for a slight trace of protein or a few red cells that persist in the urine for months or years Of course, such individuals should avoid dietary as well as other sorts of excesses, though I know of no actual case of this nature in which a relapse could be traced to rash indulgence in food or drink

If the patient fails to improve after the initial period, the diet must be regulated according to the manifestations present. Edema calls for salt restriction, while renal insufficiency with its threat of uremia requires that

passed, increasing the fluid intake may raise the urinary volume, but if it does not, care should be taken not to embarrass the heart and produce edema by excessive intake of fluid which is not excreted.

Intravenous Infusions.—In patients who, because of vomiting or for other reasons, are unable to take adequate volumes of fluid by mouth, the intravenous drip may avert dehydration and increase the urinary output. Usually, 5 per cent dextrose solution given at a rate of 30 or 40 drops per minute is the most useful. Recently I have been using the 10 per cent fructose solution which has become commercially available; more energy is obtained from the same fluid volume. Unless there is salt depletion as

noses. Following the operations, he observed improvement, which he attributed to the relief of tension resulting from the splitting of the renal capsule. The operation was popularized by Edebohls,[14] and since then th ... of reports, particularly in the surgical lit ...

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... to the operation, and there have also been numerous ... failure.

... does good, it cannot be due entirely to the relief ... Volhard ... who has reported excellent results, believes them to be due to the ... al of the sympathetic plexuses around the renal artery that is carried out in decapsulation, i e, a periarterial sympathectomy of the renal artery. That decapsulation does aid the circulation through the kidney is indicated by the experiments of Huelse and Litzner,[18] who found that decapsulation increases the circulation through the kidney of the dog.

Volhard believed that the operation should be performed when complete or nearly complete anuria has persisted for three days, which is rare in acute glomerulonephritis. In the few cases that I have seen, in which decapsulation was performed for nephritic anuria, there was no notable ...

... that decapsulation actually helps in acute glomerulonephritis and has not advised the operation in a number of years

Caudal Anesthesia —Because caudal anesthesia has been used to reduce the blood pressure in the hypertension of eclampsia gravidarum, Hughes[19] and his associates employed it in four patients with hypertension due to acute glomerulonephritis They were able to produce repeated transitory

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marked increase in hematuria and sometimes in other symptoms Tonsillectomy should be postponed until two or three months after the patient has recovered or until improvement has become very slow or stopped. Even in such cases, the possibility of some exacerbation, notably of hematuria, must be borne in mind In glomerulonephritis, contrary to focal

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checked the progress of the disease and reexamination one to twelve years

Cortisone and ACTH.—In view of the remarkable effect of these hormones in rheumatic fever, there seemed reason to anticipate that they would also be of value in acute glomerulonephritis. So far, these hopes have not been attained to any notable extent. Farnsworth[73] reported on three children with acute and subacute glomerulonephritis treated with ACTH. There was a favorable effect on hematuria, azotemia and hypertension. Contrariwise, Heller *et al.*[83] did not find that cortisone affects the proteinuria or hematuria of acute and subacute glomerulonephritis in any consistent fashion. The writer has seen improvement in urinary findings that seemed to be correlated with the administration of these hormones in some cases, but the effect did not long outlast the medication and in some patients ceased while the hormone was still being administered. More often, there is no effect and sometimes urinary findings and hypertension become aggravated with the administration of the hormone. There does not seem to be good evidence that these hormones alter the natural history of the disease and from what is now known their administration does not appear indicated. During hormonal administration, salt restriction should be rigorous.

Antihistamine Drugs.—In view of the role of allergic mechanisms in the pathogenesis of acute glomerulonephritis, one might anticipate that antihistaminics would be of value This does not seem to be the case. The writer has used pyribenzamine and other antihistamine drugs in acute nephritis without benefit. Lawson[74] gave pyranisamine malleate to alternate patients in a series of 33 cases of acute glomerulonephritis. The patients given the antihistamine drug were consistently slightly slower in recovering.

Diuretics.—Almost all the known diuretics have been tried in acute glomerulonephritis. The purine bodies, notably diuretin and aminophyllin, were the most widely used. As a rule, they do not increase the urinary output and seem to be valueless. Mercurial diuretics rarely produce appreciable diuresis during the oliguric stage of acute glomerulonephritis. Indeed, they may be followed by decrease in urinary volume and by increase in hematuria. While mercurials are ordinarily innocuous to the renal epithelia, this may not be true in acute glomerulonephritis. For these reasons, I do not use mercurials in acute glomerulonephritis. I twice saw death from mercurial colitis as a result of the use of the now obsolete novasurol in patients with impaired renal function Ammonium and calcium chlorides are inefficient in acute glomerulonephritis, and moreover may produce severe acidosis if renal function is poor. Hypertonic *sucrose* solution (100 cc. of a 50 per cent solution by vein) sometimes produces profuse diuresis in acute glomerulonephritis, as was seen several times when it was given for edema of the brain However, I have several times observed that it may fail when the oliguria is very severe and, in view of the possible tubular damage (page 361) no longer use it

Dialysis.—The use of the artificial kidney and other methods of dialysis of the blood is discussed on page 237.

Surgical Treatment.—Decapsulation of the kidney in patients with glomerulonephritis was first carried out by Harrison,[75] who operated on 2 cases of acute and 1 of subacute glomerulonephritis under mistaken diag-

noses. Following the operations, he observed improvement, which he attributed to the relief of tension resulting from the splitting of the renal capsule. The operation was popularized by Edebohls,[n] and since then there has been a considerable number of reports, particularly in the surgical literature, of cases of very severe acute glomerulonephritis in which rapid improvement has followed decapsulation. However, in at least a majority of these cases it is not clear that the improvement is actually attributable to the operation, and there have also been numerous reports of complete failure.

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the experiments of Huelse and Latzner,[n] who found that ... ion increases the circulation through the kidney of the dog.

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Caudal Anesthesia —Because caudal anesthesia has been used to reduce

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reductions in blood pressure by this measure ...

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... *tonsillectomy should not be carried out during the acute stage of glomerulonephritis* When the operation is performed at this period, there is often marked *increase in hematuria* and sometimes in other symptoms. Tonsillectomy should be postponed *until* two or three months after the patient has recovered *or until* improvement has become very slow or stopped Even in such cases, the possibility of some exacerbation, notably of hematuria, must be borne in mind In glomerulonephritis, contrary to focal nephritis (see page 661) one rarely ...

... the progress of the disease and reëxamination *one to twelve years*

later showed no evidence that the children with acute glomerulonephritis who had had their tonsils removed fared better than those who still had them. If the operation is performed, penicillin should be given.

What has been said about tonsillectomy also applies, in general, to the surgical treatment of sinus infections. The latter is rarely called for since antibiotics have been available.

Physiotherapy.—Eppinger[81] reported excellent results in acute glomerulonephritis from diathermy of the renal region. He saw almost immediate diuresis in two patients with extreme oliguria. In the only two cases in which I have seen diathermy used, the results were entirely negative. Roentgen irradiation of the kidneys has also been recommended (see Salvioli[82]); it has had no effect in the few instances I have seen it used.

Treatment of Individual Manifestations.—The heart and blood pressure must be carefully watched throughout the course of acute glomerulonephritis. Whenever there is evidence of cardiac insufficiency, digitalis should be given. Hypertension is not a contraindication to digitalis In acute left ventricular failure with massive pulmonary edema, the patient should be propped up, morphine given and tourniquets applied to the extremities so as to trap blood in them. Lanatoside C (Cedilanid) is then given intravenously to the previously undigitalized adult in dosage of 1 to 1.5 mg. In patients who have not been digitalized 0.3 mg. of crystalline strophanthin may be given intravenously; it is highly praised by Continental clinicians but I have seen no advantages over lanatoside C and it is perhaps not as safe. If the arterial pressure falls, caffein may help. However, the most effective measure in acute myocardial failure with pulmonary edema is generally *venesection*. As much as 500 cc. may be taken from vigorous adults and proportionate amounts from children. Smaller quantities, as 200 cc., should be removed from individuals who have been debilitated by preceding illness. Needless to add, in the presence of cardiac insufficiency one should never fail to look for pleural or other serous effusions, and remove them if present

Pains in the kidney region may be alleviated by hot applications, belladonna or mustard plasters, codein may be required

The treatment of uremia, edema, and hypertensive encephalopathy is discussed in the respective chapters.

Duration of Bed-rest.—The patient is to be kept in bed until edema and hypertension have disappeared, renal function has returned to normal, and the urine has become free of protein and formed elements, even though this takes several weeks. Hyposthenuria often lasts for months without being indicative of chronic disease and does not call for prolongation of bed rest There are cases (see above) in which either slight proteinuria or microscopic hematuria persists indefinitely after the patient is apparently well in all other respects If examined a year or two later, such patients usually have normal urine, but some go on to the gradual development of chronic glomerulonephritis. In some patients proteinuria persists for a decade or more with no other evidence of disease. Included in this group are those cases which have no proteinuria while in bed, but develop it in the erect posture. There seems to be no good end attained by keeping these patients in bed more than a week or two after they are left with only such residual

changes,

for a few days after leaving bed, but then the

its former level.

If the patient with residual manifestations of acute glomerulonephritis can afford it, it may be well for him to go for several months during the winter to a warm and dry climate.

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28 Bradley Am J Med. 7, 389, 1948
29 C
30
31
32 , 44, 1928
33 Lichtwitz Reference 25, p 121
34 Litzner Ztschrft f klin Med *112*, 93, 1929
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later showed no evidence that the children with acute glomerulonephritis who had had their tonsils removed fared better than those who still had them. If the operation is performed, penicillin should be given.

What has been said about tonsillectomy also applies, in general, to the surgical treatment of sinus infections. The latter is rarely called for since antibiotics have been available.

Physiotherapy.—Eppinger[31] reported excellent results in acute glomerulonephritis from diathermy of the renal region. He saw almost immediate diuresis in two patients with extreme oliguria. In the only two cases in which I have seen diathermy used, the results were entirely negative. Roentgen irradiation of the kidneys has also been recommended (see Salvioli[52]); it has had no effect in the few instances I have seen it used.

Treatment of Individual Manifestations.—The heart [illegible]

[illegible] hypertension is not a contraindication to digitalis. In acute left ventricular failure with massive pulmonary edema, the patient should be propped up, morphine given and tourniquets applied to the extremities so as to trap blood in them. Lanatoside C (Cedilanid) is then given intravenously to the previously undigitalized adult in dosage of 1 to 1.5 mg. In patients who have not been digitalized 0.3 mg of crystalline strophanthin may be given intravenously; it is highly praised by Continental clinicians but I have seen no advantages over lanatoside C and it is perhaps not as safe. If the arterial pressure falls, caffein may help. However, the most effective measure in acute myocardial failure with pulmonary edema is generally *venesection*. As much as 500 cc may be taken from vigorous adults and proportionate amounts from children. Smaller quantities, as 200 cc, should be removed from individuals who have been debilitated by preceding illness. Needless to add, in the presence of cardiac insufficiency one should never fail to look for pleural or other serous effusions, and remove them if present.

Pains in the kidney region may be alleviated by hot applications, belladonna or mustard plasters, codein may be required.

The treatment of uremia, edema, and hypertensive encephalopathy is discussed in the respective chapters.

Duration of Bed-rest.—The patient is to be kept in bed until edema and [illegible]

hematuria persists indefinitely after the patient is apparently well in all other respects. If examined a year or two later, such patients usually have normal urine, but some go on to the gradual development of chronic glomerulonephritis. In some patients proteinuria persists for a decade or more with no other evidence of disease. Included in this group are those cases which have no proteinuria while in bed, but develop it in the erect posture. There seems to be no good end attained by keeping these patients in bed more than a week or two after they are left with only such residual

Chapter

21

CHRONIC GLOMERULONEPHRITIS

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of chronic glomerulonephritis has been recognized only within recent years
Formerly, those cases of chronic glomerulonephritis in which edema is the outstanding feature were grouped with chronic nephrosis under the name of "chronic parenchymatous nephritis" On the other hand, the glomerulonephritides which are dominated clinically by cardiovascular phenomena
. . . the term "chronic
. . .

Ellis's Type 1 and Type 2 Nephritis.—Longcope[1] and his associates pointed out that glomerulonephritis "may assume two more or less distinct forms." The earliest stages of what they termed type A have the clinical picture here described under the designation of acute glomerulonephritis, follow an acute infection, and terminate in recovery in a high proportion of the cases Type B is usually insidious in onset, is not preceded by an obvious acute infection though there is usually some chronic indolent infection of the tonsils or sinuses, runs a chronic course dominated by edema, and

. . .

most recent clinicians and in this book He believes these to be "two different disorders," which he designates as type 1 nephritis and type 2 nephritis. Ellis differentiates the two disorders as follows:

In type 1 nephritis, the onset is usually abrupt and accompanied by such general symptoms as malaise, vomiting and headache Hematuria is present at the onset, there is a history of antecedent infection in 84 per cent, edema is of short duration, 60 per cent of the cases occur in the first

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83. HELLER, JACOBSON and HAMMARSTEN: J Lab & Clin Med, *37*, 133, 1951

The relations of pregnancy to chronic glomerulonephritis are considered in Chapter 32.

The severity of the acute attack is by no means a reliable index of the likelihood of *chronicity*, for chronic disease may evolve from very mild initial attacks. Leaving bed too early during subsidence of the acute attack h ... ted as favoring chronicity, but this is not proved. The ques ... developn ...

While there are many cases of ... stage occurs under our eyes or can be traced ... large contingent in ... We see the patient ... for the ... nephriti ... renal di ... mild th ... injury ... insignificant "cold" for which a physician was not consulted. Possibly, also, some of the cases date from scarlet fever in childhood. The *situation* is closely analogous to that encountered in many cases of mitral stenosis which, we know, have evolved from an antecedent rheumatic infection, even though there is absolutely no history of the latter. As is the case with chronic valvular disease, the "cryptogenic" cases of chronic glomerulonephritis are more common in adults than in children; in the latter, a history of the initial attack can be obtained in a high proportion of the cases. On the other hand, such a history is obtainable in only a minority of adults with chronic glomerulonephritis.

Chronic glomerulonephritis occurs at all ages, but it is predominantly a disease of the earlier periods of life. This is illustrated in the following table of 54 cases of chronic glomerulonephritis which came to necropsy at the Mount Sinai and Montefiore Hospitals:

Age at death, yrs	*No. of cases*
1 to 10	7
11 to 20	11
21 to 30	15
31 to 40	9
41 to 50	9
51 to 60	2
61 to 70	1
Over 70	0

Almost one-half of the cases terminated in the second and third decades.

PATHOGENESIS OF CHRONIC GLOMERULO-NEPHRITIS

It is not definitely known why certain cases of acute glomerulonephritis become chronic while others heal completely. In most infectious diseases, chronicity is the result of the persistence of the etiologic organism in the lesions. But we have seen that the lesions of acute glomerulonephritis do

two decades, and 82 per cent recover. The histological changes described by Ellis are those here presented as the lesions of acute and chronic glomerulonephritis. Ellis stresses that in the cases which die early the glomerular lesion is diffuse and necrosis of the afferent arterioles may be prominent, while in the later stages there are superadded focal changes secondary to lesions of the arteries which may go on to fibrosis.

In type 2 nephritis the onset is insidious without the general symptoms observed in type 1. Hematuria is absent or slight, a history of previous infection is obtained in less than 5 per cent, edema is persistent and the dominant feature, the incidence is similar in all decades, and less than 5 per cent recover. There were no histological observations on cases dying in less than a month after the known onset. Those succumbing during the [illegible] on to hyalinization which affected both the capillary basement membrane and the intercapillary stroma. Lesions secondary to changes in the renal arteries are rarely seen. The fibrosis that develops is diffuse.

To the writer, it appears that Ellis's type 1 nephritis represents those cases of glomerulonephritis which are still in the initial acute stage or in which the latter is recognizable in the history. Type 2 nephritis seems to include both cases of chronic (lipoid) nephrosis and of glomerulonephritis in which the acute stage went unrecognized—and there are many of the latter. Ellis states that of 145 cases of type 2 nephritis there are "some 12 cases which on both clinical and histological grounds would be called nephrosis by many observers." Ellis does not accept the concept of nephrosis as a separate entity. The reasons why the writer believes that there is an entity of chronic nephrosis distinct from glomerulonephritis are summarized beginning on page 462. There it is pointed out that not only glomerulonephritis but also lipoid nephrosis may go on to glomerular hyalinization with hypertension and renal insufficiency—failure to recognize that this may occur in lipoid nephrosis is one of the reasons why the independent existence of the latter has been denied.

ETIOLOGY AND OCCURRENCE OF CHRONIC GLOMERULONEPHRITIS

The etiology of acute glomerulonephritis, from which the chronic form evolves, has been discussed (page 529). Chronic glomerulonephritis seems more apt to develop after certain varieties of the acute disease than following others. Thus, postscarlatinal glomerulonephritis becomes chronic in only an exceedingly small proportion of the cases Chronic glomerulonephritis is more likely to evolve when the acute attack follows sore throat Most of the cases of diffuse glomerulonephritis occurring in subacute bacterial endocarditis reach the chronic stage if the patient lives long enough. According to the descriptions of Osler, Nobécourt and others (page 535), and my own experience, glomerulonephritis complicating the erythema group of diseases is quite likely to become chronic Evidence was quoted in the preceding chapter that acute glomerulonephritis in older individuals is decidedly more apt to become chronic than in the young

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for the first time when he already has an obviously ... nephritis and does not recall any symptoms which would indicate previous renal disease In such cases, it is probable that the acute attack was so mild that it never came to the attention of the patient. The initial renal injury may have followed a sore throat which was considered merely an insignificant "cold" for which a physician was not consulted. Possibly, also, some of the cases date from scarlet fever in childhood. The situation is closely analogous to that encountered in many cases of mitral stenosis which, we know, have ... infection even though there is ab... chronic valvular diseas... nephritis are more co... history of the initial a... cases On the other h...

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not result from the actual invasion of the kidney by bacteria. Some factor other than settling of microörganisms in the kidney must therefore operate to produce chronicity in glomerulonephritis. The nature of this factor, which may be renal or extrarenal, is not definitely established, but several possibilities enter:

1. *Persistence or Exacerbation of the Extrarenal Focus.*—There is much evidence that persistence or exacerbation of the original or another extrarenal infective focus may cause chronicity or exacerbation of chronic glomerulonephritis. Exacerbations of the inflammatory process in this focus (*e. g.*, the tonsils) are accompanied by hematuria or other evidences of lighting up of the glomerulonephritis. The process would thus be analogous to what is so frequently observed in rheumatic valvular disease, in which renewed sore throats are each accompanied by further injury to the already damaged valve. "The patient does not suffer from one attack of nephritis but from one thousand and one," says Emerson,[3] who has observed clinical evidence of the exacerbations. In patients with chronic glomerulonephritis, one not uncommonly observes that an intercurrent sore throat results in flaring up of the disease, as manifested by hematuria and impairment of renal function and less often edema or rise in blood pressure.

As Bell and Hartzell[4] point out, anatomical evidence affords strong support for the occurrence of repeated fresh exacerbations in many cases, for one often sees besides old lesions, signs of more recent injury. Such a conception explains why so small a proportion of cases of postscarlatinal glomerulonephritis becomes chronic—*for here no focus is usually left*—while a much greater proportion of the cases that follow tonsillitis results in the chronic disease. But in cases in which glomerulonephritis follows tonsillitis, removal of the tonsils does not prevent the progression of the renal process; the general experience here is much the same as in rheumatic valvular disease. Possibly, once the kidney has been injured it is more susceptible to injury from any infectious focus in the period before *complete* recovery This is not true after *total* healing, for then recurrence of glomerulonephritis is an extreme rarity

Support for the theory that chronicity of glomerulonephritis is a result of persistence of activity in the extrarenal focus of infection is afforded by the observations of Winkenwerder, McLeod and Baker.[1] They found that in cases [illegible]
the numl [illegible]
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in recovery than when the renal mischief complicated a chronic infection

Further evidence that activity of an infective focus is concerned in some cases of chronic glomerulonephritis has been afforded by observations on exacerbations. Studying 28 exacerbations (marked by increased hematuria and usually by further impairment of renal function) in 13 patients with chronic glomerulonephritis, Seegal *et al.*[5] found that an infection, usually with Group A hemolytic streptococci, preceded the exacerbation by one to four days. Earle[6] and his associates observed rise in the antistreptolysin titer in 24 of 33 exacerbations in chronic glomerulonephritis; in 6 there was no rise and in 3 the data were inconclusive.

2. *Intrinsic Progressiveness of the Glomerular Lesions.*—In many patients, omerulonephritis progresses to renal insufficiency over a period of years uring which there is no evidence of infection. There may be no history f a sore throat for years, examination of the upper respiratory tract and nuses by a specialist is negative, and the antistreptolysin titer is not levated Accelerated sedimentation of the red cells is not necessarily ... may result from changes in the plasma

infection may have carried in themselves the seeds of progr... original proliferative changes in the walls of the glomerular loops and ... of the basement membranes may be so great

ischemic atrophy of renal parenchyma. Patients with chronic glomerulo-nephritis may develop very high blood pressure and the clinical picture of malignant hypertension At necropsy, necrotizing arteriolar lesions are found in the kidney In these cases the sequence of events apparently is that the glomerulonephritis leads to the hypertension, and the latter is correlated with the arteriolar and arterial lesions. Sometimes, the arteriolar

disease, slowly with arteriolar sclerosis and endarteritis obliterans, fulminantly in the case of arteriolar necrosis.

In the slowly progressive cases without evidence of a persistent infective focus, the other factors are presumably predominant Arteriolar and arterial changes become important especially in the older age groups and where hypertension is pronounced

PATHOLOGICAL ANATOMY OF CHRONIC GLOMERULONEPHRITIS

The anatomical picture encountered at necropsy varies with the period of time that has elapsed between the acute glomerulonephritis and death, which may be from a few months to several decades. While in the acute

to produce chronicity in glomerulonephritis. The nature of this factor, which may be renal or extrarenal, is not definitely established, but several possibilities enter:

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the numbe[illegible]
during prog[illegible]
an acute infection with systemic reaction was much more apt to terminate in recovery than when the renal mischief complicated a chronic infection

Further evidence that activity of an infective focus is concerned in some cases of chronic glomerulonephritis has been afforded by observations on exacerbations. Studying 28 exacerbations (marked by increased hematuria and usually by further impairment of renal function) in 13 patients with chronic glomerulonephritis, Seegal *et al.*[5] found that an infection, usually with Group A hemolytic streptococci, preceded the exacerbation by one to four days. Earle[6] and his associates observed rise in the antistreptolysin titer in 24 of 33 exacerbations in chronic glomerulonephritis, in 6 there was no rise and in 3 the data were inconclusive.

ubstance. The degree of contraction may be extreme, so that the weight f both kidneys in an adult is less than 75 grams All sizes between such mall organs and the normal are met with In fact, there are slightly enlarged granular kidneys, evident than compensated for the lost par

seen on occasion, but are not as common as in the primary kidney.

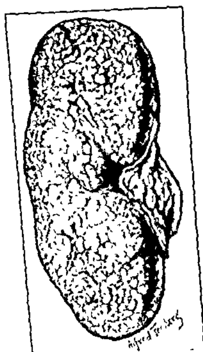


Fig 27 – Chronic glomerulonephritis in the stage of secondary contraction, uniform granulation of the surface

On section of the kidney, which offers increased resistance to the knife, it is seen that all parts of the organ are shrunken The cortex is narrowed and irregular, so that in places the pyramids may practically reach the

tracted kidneys In fact, it is far from uncommon that one is unable to

over, as br[illegible] c-
companied [illegible] [illegible]od
vessels. Thus, exceedingly complicated and variegated pictures are the rule.

Macroscopic Appearance.—When glomerulonephritis has lasted from a few months to as much as three or four years, the most frequent finding is the "large white kidney," as it was termed by Wilks,[8] a gross appearance that also occurs in chronic nephrosis. The kidneys are enlarged and their weight may exceed even double the normal, though this is exceptional. The consistency is soft. The capsule strips readily without damage to the kidney substance. The surface is usually pale and of a yellowish or grayish-white color. In the presence of marked congestion, the color is more brownish. Small hemorrhages are found quite frequently and may be very numerous.

On section, the parenchyma swells above the edge of the capsule. The cortex is broadened and the markings obscured; the cortical substance appears moist and shiny, of a color similar to that of the surface. There are often areas of deeper yellow lipoid change. In instances in which the deposition of fat and lipoid in the tubules is very great, the entire section presents a uniform buttery-yellow color and greasy feel (myelin kidney of McNee[9]). Some of the glomeruli are enlarged, appearing as grayish, translucent points; others may be hemorrhagic. Hemorrhages may be present as streaks or dots. The medulla is well demarcated from the cortex by its deeper, brownish-red color.

The picture of the large white kidney just sketched corresponds to the stage of glomerulonephritis in which the changes consist predominantly in inflammatory lesions of the glomeruli and secondary degenerative changes in both glomeruli and tubules There is then a gradual but radical alteration in the picture as the specific renal elements are completely destroyed and disappear. Their place is taken by connective tissue (replacement fibrosis) which gradually shrinks with resultant contraction of the kidney. The intact glomeruli and, much more strikingly, their appertaining tubules, hypertrophy. Islands of such hypertrophied elements protrude above the surface to constitute the well-known granules It is thus that from the large, soft, smooth kidney of the earlier stages there develops the small, hard, granular organ long known as the "secondary contracted kidney" because it evolves from a previously enlarged kidney. The time required for this transformation varies. Sometimes, well-marked contraction and granulation are encountered when the disease has lasted but two or three years, while in other cases there may be little or none after even five years. Evidently, the "tempo" of the process varies from one case to another, probably, also, the number and severity of the acute exacerbations and the degree of arterial change also play parts.

The fully developed secondary contracted kidney is a small, hard, granular organ from which the thickened capsule is removed with some difficulty and often only at the expense of taking along bits of the cortical

* For what is known of the architecture of the kidney in chronic Bright's disease, the reader is referred to the pioneer and classic investigations of Oliver,[7] in which he studied individual nephrons isolated by micro-dissection

Depending on whether or not epithelial proliferation with formation of [illegible] and others have differ-

[illegible] crescents. To indicate that the extracapillary cases present a [illegible] and rapidly fatal clinical picture than those with only intracapillary lesions, Loehlein speaks of stormy and mild types Such a distinction is by no

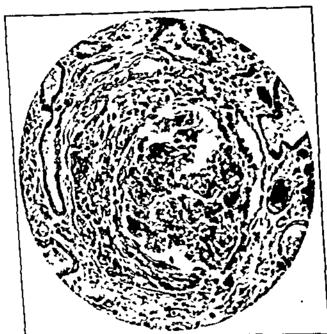


FIG 28 —Malpighian body in subacute glomerulonephritis Proliferation of capsular epithelium resulting in crescent formation, also, changes in the glomerular tuft.

means universally true, but in general it seems that extracapillary glomerulonephritis is usually found in cases which have succumbed relatively quickly to renal insufficiency, while the cases with largely intracapillary lesions tend to a more protracted course Quite possibly, compression of the glomerular tuft, which is often obvious in the sections, serves to accelerate the onset of renal insufficiency, though presumably the intracapillary process is especially severe in cases in which the epithelial reaction is so marked

decide from the gross appearance whether he is dealing with a primary or a secondary contracted kidney. The pelvic fat is increased in quantity.

Microscopic Picture.—It has been seen (page 548) that in the first stages of glomerulonephritis, the changes are confined to the glomerular capillaries. If the disease lasts a longer time, these lesions within the glomerular tuft progress and the other renal structures become implicated. In some cases the capsular epithelium undergoes inflammatory proliferation. The tubules very soon show *degenerative changes.* In the course of time the lesions of the affected glomeruli and tubules lead to their obliteration and disappearance. Such *parenchyma as survives hypertrophies in an effort* to compensate for the destroyed elements. [illegible] architecture of the kidney. The particular picture encountered depends on the stage of the progress at which death has occurred. We shall follow individually the progress of the lesions in each of the renal structures.

MALPIGHIAN BODIES.—[illegible] the early stages; in fact, [illegible] which appears normal. [illegible] found in the acute stage [illegible] to be seen. The glomerulus is enlarged, due to swelling and proliferation of the capillary endothelium and glomerular epithelium and the lumens of the capillaries are further blocked by the accumulation of albuminous exudate and leukocytes. Such glomeruli are altogether or almost bloodless. *In other glomeruli,* however, it is seen that the circulation has been reëstablished through at least some of the loops and these are congested with blood. The capsular spaces of many of the glomeruli contain coagulated exudate, fibrin, red blood cells, leukocytes and desquamated epithelia; capsular adhesions are present in places.

In addition to the above changes in the glomerular tuft, there is proliferation of the capsular epithelium in many of the cases which come to necropsy at any time from weeks to years after the onset. This results in the formation of crescentic masses of epithelial cells known as *epithelial crescents.* According to McGregor,[10] the inner layers of the crescent are sometimes formed by proliferated and desquamated glomerular epithelium. Such epithelial crescents may have a thickness of several layers of cells, compress the tuft and even proliferate into the mouth of the urinary tubule. Later, the cells of the crescents undergo fatty and other degenerative changes, desquamate, and organization by connective tissue from without occurs. (A different interpretation is given by Bell[11] and Allen,[12] who believe the epithelial cells are transformed into fibroblasts and form the fibers.) Sometimes, there are numerous spaces within the crescents which communicate with the free part of the capsular space. While the presence of crescents is usually an indication that the glomerulonephritis is of relatively short duration (subacute), they may also be found in older cases, being here presumably the result of comparatively recent acute exacerbations. Thus, I saw abundant crescent formation in a case known to have been of over five years' duration. A few crescents, usually small, are not uncommon in old secondary contracted kidneys.

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ontracted kidney. Ultimately, however, the hyaline . . . secondary contracted kidneys

. . .
traces demonstrable through the microscope.

TUBULES.—The tubules are involved in all the stages of chronic glomerulonephritis. In some instances, the tubular lesions are not striking for a

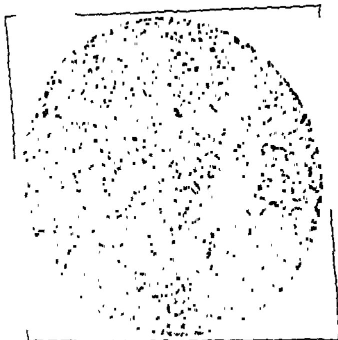


FIG 30 —Chronic glomerulonephritis with renal insufficiency Two hypertrophic glomeruli surrounded by islands of tubules in a state of compensatory hypertrophy and dilatation

considerable period but, as a rule, they quickly become evident. At a very early stage hyaline-droplet and more particularly fatty and lipoidal alteration of the tubular epithelium appears. It is usually at its maxi-

but any part may be affected As a rule, the changes are diffuse, but occasionally only scattered groups of tubules are involved There is more or less desquamation of tubular epithelia, which *are found in the* lumens together with casts, red and white blood cells and cellular detritus Scattered necroses are seen at times but are not prominent.

Such of the glomeruli as do not recover from the acute inflammatory process undergo hyaline degeneration. The walls of the affected glomerular capillaries together with their contents are conv [illegible] According to her description, as the process advances these hyaline fibers increase in number and thickness, and finally fuse with one another and the basement membrane of the capillary. Hyaline thickening of the capillary wall (capillary basement membrane?) also contributes. The process of hyalinization advances with varying rapidity in different

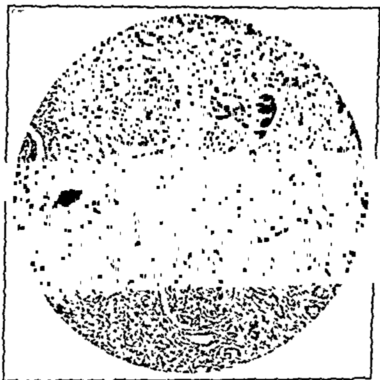


Fig 29—Chronic glomerulonephritis. Two glomeruli showing intracapillary changes with secondary degeneration and atrophy of tubules and replacement fibrosis

capillaries, so that small hyaline areas appear in various parts of the glomerulus while the remaining portions are still very rich in nuclei, the whole presenting a very characteristic appearance. Gradually, the hyaline areas fuse, the number of nuclei diminishes, and, finally, a homogeneous hyaline sphere remains. At the same time, the capsule undergoes fibroid transformation as described above. The hyaline glomerulus is thus often surrounded by a concentrically laminated ring of connective tissue which ultimately also becomes hyaline and fuses completely with the hyaline glomerulus. The hyaline glomerulus and fibroid capsule can often be told apart for a long time by the difference in the staining, particularly in the Van Gieson preparation. At one stage of the process, the hyaline glomeruli

requisite adaptation Volhard[18] pointed out that ...
vigorous diuresis exhibit tubules which are dilated and lined by low

from their appertaining glomeruli by scarring processes. ...
the aglomerular tubules are nourished by a branch (known as Ludwig's vessel) which leaves the afferent arteriole before it reaches the glomerulus and, by-passing the latter, empties into the peri-tubular capillaries. Other arterial branches also extend from the interlobular and even larger arteries directly to the network surrounding the tubules. Oliver's investigations reveal that all these arterial vessels which by-pass the glomeruli are rare and functionally insignificant in health, except perhaps in old age, but are

individual nephrons More plausibility is lent to the conception of the functioning of aglomerular tubules in chronic renal disease by the existence of aglomerular kidneys in certain fishes and especially, as pointed out by Oliver, by Grafflin's[19] finding that the daddy sculpin begins life with a glomerular kidney which is then converted into a purely tubular organ by destruction of the tufts

THE INTERSTITIUM —From an early stage, there is proliferation of the interstitial connective tissue As the tubules atrophy, their place is taken by connective tissue (*replacement fibrosis*) *It is this extensive interstitial fibrosis* that led to the old term "chronic interstitial nephritis," but Weigert (see Chapter 13) long ago showed that the interstitial changes are secondary to those in the specific renal elements The connective tissue contains large numbers of lymphocytes and mononuclear wandering cells

refractile lipoids identical with those occurring in chronic nephrosis (page 449) are found In the advanced stages, large areas of connective tissue separate the isolated islands of functioning parenchyma, in these are the atrophic remnants of tubules and the hyaline vestiges of glomeruli.

With complete obliteration of glomeruli, the appertaining tubules gradually atrophy and collapse. They are seen as little groups of epithelial cells in the midst of the large areas of replacement fibrosis which occupy the greater portion of the field in the secondary contracted kidney. Small areas of tubular atrophy are often present in cases of but a few months' duration.

Attempts to regenerate the destroyed tubules become manifest at a relatively early stage. The newly-formed cells are often unusually large and have deeply staining nuclei. Not uncommonly, the efforts at regeneration lead to the formation of atypical tubules of irregular shapes. Rarely,

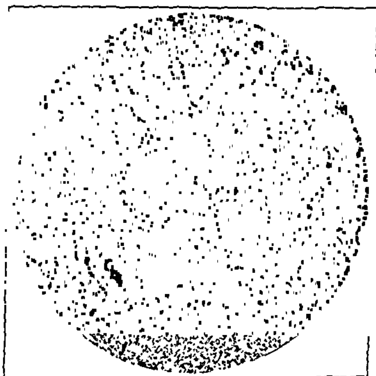


FIG 31.—Chronic glomerulonephritis in stage of secondary contraction Hyalinized glomeruli, extensive replacement fibrosis and an island of compensatory tubular hypertrophy and dilatation

giant cells are formed or the regenerative process may lead to the formation of minute adenomata.

In cases in which widespread destruction of renal elements has produced protracted and severe impairment of renal function, there are usually islands of dilated tubules lined by strikingly low, sometimes almost flat, epithelium. The connection of these dilated tubules with hypertrophied glomeruli is generally evident. Such islands often constitute the fine granulations of the surface. It is probable that the dilatation of the surviving tubules is a manifestation of the way in which they function. The number of surviving nephrons in such kidneys appears to be proportionately much more reduced than is the volume of filtration, and the ultimate

Var
nephr

... not the primary ...

are accompanied by endarteritis and arteriolar ...
phase of essential hypertension. Volhard[22] believes that the endarteritis in
... is the result of the angiospasm which he

however, that the ...
of glomerulonephritis is not convincing
... able that the endarteritis is the consequence of the

of such vessels as the umbilica
thickening due to connective-ti
the internal elastic membrane
tis that occurs in chronic glomerulonephritis, and it would seem that the cause of the endarteritis that occurs in this condition is akin to that in ligation experiments, namely, obstruction to the flow of blood

Hypertrophy of the Muscular Layer.—Hypertrophy of the muscular layer of the arteries was first noted by Johnson[25] and confirmed by the measurements of Ewald.[26] Volhard observed that it is found in glomerulonephritis but not in essential hypertension. I have been able to confirm these observations in a large number of cases, except that in some instances of the malignant phase of essential hypertension the media also appears hypertrophic. The muscular hypertrophy is found in cases of glomerulonephritis of several years' duration in which the hypertension has been severe. It is not seen in early cases. Occasionally, the arterioles in old secondary contracted kidneys have medial hypertrophy, but in most such cases there is distinct and often marked medial atrophy with the development of arteriolosclerosis. The vessels of the kidney affected are those of all sizes down to and including the interlobular arterioles. I have not found muscular hypertrophy in the arterioles of other organs than the kidney (but see the findings of Kernohan, Anderson and Keith in essential hyper-

of the larger arteries, as the radial, is hypertrophied in chronic glomerulonephritis

ARTERIOLAR LESIONS.—Arteriolar lesions are prominent features of many instances of chronic glomerulonephritis. Rare in cases of short duration, they become more common the longer the disease lasts, and are a regular finding in long-standing cases. The great frequency of arteriolar lesions in long-standing chronic glomerulonephritis is illustrated by the findings of Horn[20] and his associates, who observed in 49 cases of chronic glomerulonephritis 14 instances of arteriolar sclerosis, 13 of what is here called endarteritis obliterans and 22 of arteriolar necrosis. Four varieties of arteriolar change are encountered in chronic glomerulonephritis:

1. Endarteritis obliterans.
2. Muscular hypertrophy.
3. Arteriolosclerosis.
4. Arteriolar necrosis.

Endarteritis Obliterans.—Endarteritis obliterans is present in almost all cases of several years' duration in which active destruction of glomeruli is still in progress. The beginnings of endarteritis obliterans are occasionally seen in cases succumbing within the first year, but it is slight Also, in old secondary contracted kidneys, endarteritis obliterans is sometimes found but is more often absent. The lesion affects the arterial vessels of all sizes in the kidneys. It consists in the variety of diffuse intimal thickening termed "regenerative connective tissue proliferation" by Jores,[21] and is identical with the intimal thickening that occurs when a vessel is ligated or in the physiological obliteration of such vessels as the umbilical vein. The thickening results from the proliferation of ordinary (collagenous) connective tissue in the intima of the vessel, the elastic membrane not being hypertrophied and reduplicated as in arteriolosclerosis If elastic tissue is found in the intima, it is in the form of fine fibrils in the midst of the collagenous fibers, but the basis of the process is the proliferation of collagenous connective tissue. Fatty and hyaline degeneration of the thickened intima is common. The connective-tissue thickening of the intima is often accompanied by endothelial proliferation, and the final result is not uncommonly complete obliteration of the lumen

It is usually easy to differentiate arteriosclerosis and endarteritis obliterans in vessels of the size of the interlobular arteries of the kidneys or larger. In such vessels, the hyperplasia of the internal elastic lamina in arteriosclerosis is striking. The differentiation is sometimes more difficult or impossible in the case of the vasa afferentia near their entrance into the glomeruli. In these, arteriolosclerosis is usually manifested solely by the subendothelial deposition of hyaline substance, and precisely the same appearance can be produced in endarteritis obliterans of these minute vessels by hyaline degeneration of the proliferated connective tissue of the intima. Fatty change may occur in either variety of intimal thickening In cases of considerable duration, endarteritis obliterans, arteriosclerosis and arteriolosclerosis may all be seen in the same kidney

Endarteritis obliterans did not occur in the vessels of other organs than the kidney in a series of cases of glomerulonephritis which I[22] examined. However, I did not study the retina, in which endarteritic changes are generally present when there is hypertensive neuroretinopathy.

are of the opinion that the arterial obliteration is of great importance in ... in chronic glomerulonephritis. It

...

nephritic process.

Arteriolar Necrosis.—This lesion occurs under two circumstances. What seems to be a necrotizing arteriolitis of at least partially inflammatory ... (hypertension may also play a part)

...

necrosis of glomerular loops.

Arteriolar necrosis in the kidneys and to a much less extent in other organs sometimes also develops in chronic glomerulonephritis in which the diastolic pressure has been very high for a protracted period This form of arteriolar necrosis would seem to be a direct consequence of the extremely high blood pressure and of the same pathogenesis as the arteriolar necrosis in the malignant phase of essential hypertension (page 683). It would appear probable that the necrosis of the renal arterioles causes further acute and severe impairment of the already damaged renal function, and thus contributes significantly to the production of the final renal failure. The clinical picture is then practically identical with that seen in the malig- ... the malignant

CLINICAL PICTURE OF CHRONIC GLOMERULONEPHRITIS

Chronic glomerulonephritis presents a great variety of clinical pictures so dissimilar that the older clinicians considered them as distinct diseases.

...

outlined briefly

Arteriolosclerosis.—Arteriolosclerosis is present in practically all cases of chronic glomerulonephritis in which there has been arterial hypertension for many years. The lesions are identical in histology and distribution with those found in essential hypertension and have been discussed on page 284.

The consequences of the arteriolar lesions for the renal parenchyma are of interest. Severe arteriolosclerosis in chronic glomerulonephritis must injure the kidney much as it does in essential hypertension. Volhard believes that endarteritis obliterans is responsible for the progression of many cases of chronic glomerulonephritis. However, endarteritis is probably of only secondary importance in this direction, for the affected vessels

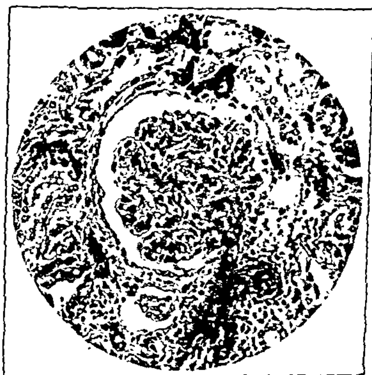


FIG 32 —Arteriolar necrosis of vas afferens in subacute glomerulonephritis The vas afferens is converted into a necrotic mass (dark in the picture) with cellular infiltration about it.

are those which lead to glomeruli that have previously been functionally impaired Arteriolosclerosis, on the contrary, may affect vessels supplying intact glomeruli and destroy them by cutting off the blood supply, precisely as occurs in essential hypertension The striking narrowing of the arterial tree of the kidney in chronic glomerulonephritis has been clearly brought out by the studies of Baehr and Ritter,[29] who injected the branches of the renal artery with a radio-opaque mixture and made roentgen-ray photographs of the organ. They found that in such preparations the

glomerulonephritis as to the primary contracted kidney.

... akin to the usual picture of the malignant phase of essential ... has long emphasized the

... generally develops. ...

dition to the usual findings in chronic ... hypertension. necrosis like that found in ... The entire picture simula ... of essential hypertension, both in the latter ... the diastolic pressure has risen to levels so high that it causes acute damage to the renal arterioles, retinopathy and perhaps edema of the brain (see page 823.)

Onset.—At times, chronic glomerulonephritis evolves under observation from the acute stage, or there is a ... usually true in children, but in adult ... when they are evidently already of ... than not, no history of an acute attack can be obtained. There are cases of chronic glomerulonephritis in which the onset and the sore throat or other infection preceding it seem typically those of acute glomerulonephritis, and only a history of a previous attack or the presence of marked cardiac hypertrophy make it probable that the present incident is an exacerbation of an old process. Rarely, necropsy first reveals that what was regarded clinically as acute glomerulonephritis was actually chronic.

Apart from the cases which start with the picture of acute glomerulonephritis, various symptoms may bring the patient with the chronic disease to the doctor. Among the common initial manifestations are headache, vertigo, swelling of the face or feet, weakness, pallor, anorexia, emaciation, nocturia, polyuria, epistaxis and shortness of breath. The very first symptoms may be of uremic origin, as nausea, vomiting, headache, mental torpor, somnolence, disorientation, pruritis or twitching. The initial examination then reveals marked nitrogen retention in the blood. Occasionally, the patient *goes first to a stomach specialist because of the onset* with gastric symptoms. On unusual occasions, convulsions or other manifestations of hypertensive encephalopathy are the first indication of the disease. Rarely, the first symptom is impairment of vision from hypertensive retinal lesions, which leads the patient to consult an ophthalmologist.

Nowadays, it is common for glomerulonephritis to be revealed first by proteinuria or hypertension discovered in an insurance or periodic physical examination.

Edema.—While edema is an important and even dominant feature in

chronic nephrosis may be impossible. Ultimately, however, impairment of renal function and hypertension appear, while the edema often regresses or disappears completely. Even this course of events may also occur in chronic nephrosis as the glomeruli become hyalinized (page 465). A not uncommon sequence of events is for the edematous stage to be followed by a variabl [illegible] h proteinuria is the onl [illegible] ment of renal function [illegible] drama. Anatomically, these cases have passed from the stage of acute glomerulonephritis through that of the large white kidney to the secondary contracted kidney.

Hypertensive Type.—Other patients emerge from the acute stage with little more than arterial hypertension. Edema may have been but slight or even totally absent and the urinary abnormalities consist in only modest proteinuria and cylindruria. For a long time, even many years, the clinical course is akin to that of essential hypertension; in fact, in older people with no history of the acute attack, the clinical differentiation of chronic glomerulonephritis from essential hypertension may be impossible. For years, the patient may feel well despite the hypertension. Eventually however, though it may be only after many years, impairment of renal function appears and the end is then usually not far off. Sometimes, though this is uncommon, cardiac failure or cerebral hemorrhage terminate the disease while renal function is still intact.

Recurrent Type.—The patient may have repeated acute attacks, with hematuria, edema and hypertension. At first, he remains with only proteinuria after the exacerbation has subsided. Finally, however, persistent hypertension and impairment of renal function appear and progress. A classical example of such a case was reported by Mann,[19] who followed the patient over a period of twenty-eight years, until he died with contracted kidneys. For the first seven or eight years after the original seizure, the patient had occasional acute attacks with bloody urine; they usually followed exposure to cold. Proteinuria was always present After this, the heart began to hypertrophy, the specific gravity of the urine gradually fell, polyuria appeared and the patient died of uremia Such an outspokenly recurrent course is unusual, but less obvious acute recurrences are very common.

Latent Type.—Following acute glomerulonephritis, the patient may remain with no demonstrable abnormality other than proteinuria, which may be but slight. The proteinuria may be unaccompanied by other symptoms for many years; not uncommonly, it is accidentally discovered in an insurance or other routine examination and there is no history of an acute attack. Such cases in which only proteinuria remains after the acute attack are known to the Germans as "Heilung mit Defekt" (healing with a defect). Some such instances seem to last for decades without any harm to the patient or very rarely eventually clear up Others, on the contrary, ultimately develop the typical picture of chronic glomerulonephritis with hypertension and impaired renal function.

The "Malignant Phase" of Chronic Glomerulonephritis.—In some cases of chronic glomerulonephritis a sequence of events occurs which

is closely akin to the usual picture of the malignant phase of essential hypertension (Chapter 26); Dr. George Baehr has long emphasized the analogy. After following one or another o

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generally develops

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examination

chronic nephrosis may be impossible. Ultimately, however, impairment of renal function and hypertension appear, while the edema often regresses or disappears completely. Even this course of events may also occur in chronic nephrosis as the glomeruli become hyalinized (page 465). A not uncommon sequence of events is for the edematous stage to be followed by a variable period, which may amount to many years, in which proteinuria is the only abnormality, until finally hypertension and impairment of renal function make their appearance—usually the final act in the drama. Anatomically, these cases have passed from the stage of acute glomerulonephritis through that of the large white kidney to the secondary contracted kidney.

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The "Malignant Phase" of Chronic Glomerulonephritis.—In some cases of chronic glomerulonephritis a sequence of events occurs which

... factors that there is no strict parallelism

When edema appears in patients with old secondary contracted ... the result of cardiac weakness and perhaps hypoproteinemia.

This is particularly true in the nephrotic type of the disease with ... nephrotic edema, in which there may be normal blood pressure over a period of years, so that the differentiation from chronic nephrosis is very difficult. However, if the blood pressure is measured daily in such patients, transitory rises to 130 or 140 mm systolic and 90 or 95 mm. diastolic pressure in a young adult confined to bed, may reveal the tendency to hypertension Particularly in children, hypertension is relatively often not demonstrable with certainty. Ultimately, even those cases which had normal blood pressure during the nephrotic stage develop hypertension. ... ulous or other cachectic

... ree, such pressures as 250 mm systolic and 150 mm diastolic are not rare. Most often, however, the

tendency is for the blood pressure to become higher, though this is by no means invariable Nor uncommonly, especially in the early stages, the *rise in the diastolic pressure is proportionately greater than that in the systolic*, so that such tensions as 170 mm systolic and 130 mm. diastolic *are encountered* But there are also cases in which the systolic rise is the more prominent

In general, the blood pressure is not as labile as in the earlier stages of essential hypertension But if the blood pressure is measured several times a day, it will almost always be found that there is considerable variation, the tendency is for the late afternoon pressure to be higher Leaving bed may also cause a rise in pressure With cardiac failure there may be a fall in blood pressure, although, except terminally, this is not seen as often as in essential hypertension In other cases, myocardial insufficiency is not accompanied by decreased blood pressure (Chapter 26)

In the recurrent cases, the blood pressure may rise with each exacerba-

plex in which cardiovascular phenomena are the central features and simulating essential hypertension

is but minimal, unless it is due to cardiac failure. In the recurrent cases, edema may appear with each exacerbation over a period of [illegible]

[illegible] ritic, nephrotic

Nephritic edema is a manifestation of active glomerulonephritis. It is, therefore, met with in the early stages and also during acute exacerbations. Sometimes such reactivation is evidenced, in addition to the edema, by the appearance or increase of hematuria. As was pointed out in Chapter 6, nephritic edema is not correlated with diminution in the protein content of the blood. While nephritic edema may be very extensive (particularly if fluid and salt are not restricted), much more often this is not the case, and the edema may be confined solely to a puffiness of the eye-lids most marked in the morning. Such bouts of slight edema are indicative of exacerbation of the glomerulonephritis.

Nephrotic edema occurs in glomerulonephritis when the patient has lost so much albumin in the urine that the albumin content of the blood is greatly diminished. Such edema is characterized by fluid extremely poor [illegible]

i. e., usually diminished total protein content, inversion of the albumin to globulin ratio, and generally increase in blood lipids. Usually, it takes several weeks or months of copious albuminuria to produce nephrotic edema. Once the edema appears, however, it is apt to be very extensive and protracted, lasting for months or even, with remissions, for over a year. If impairment of renal function appears, the proteinuria usually diminishes, the blood proteins consequently rise, and the edema clears up, though the patient is really worse.

In cases of the nephrotic type of glomerulonephritis followed from the initial acute attack, the following sequence of events may be observed: Edema appears at the very onset. This nephritic edema is usually slight and of brief duration; it occurs in the absence of either hypoproteinemia or heart failure Subsequently—and this may be after weeks, months or years—the albuminuria depletes the plasma albumin and nephrotic edema appears. The edema at this stage is often massive, that it is nephrotic is revealed by the hypoproteinemia and the absence of nephritic activity as shown by the paucity of red cells in the urine.

Of course, such a schematic course of events is not the rule in chronic glomerulonephritis, though I have seen many cases in which the precise sequence just described could be followed. More often, the factor of capillary damage due to nephritic activity is still present after the plasma proteins have been depleted by the copious and protracted albuminuria The "activity" of the nephritic process in the capillaries is demonstrated by the presence of red blood cells in great or moderate number in the urine. There is thus a combination of nephritic and nephrotic edema in the same patient, and, as a result of the hypertension and perhaps myocardial damage, cardiac weakness may ensue and also tend to cause edema. It is because of the

intervention of these other factors that there is no strict parallelism between the lowering of the blood proteins and the extent of the edema—a ... investigators, mistakenly I believe, to depreciate

When edema appears in patients with old secondary contracted kidneys, it is usually the result of cardiac weakness and perhaps hypoproteinemia.

This is particularly true in the nephrotic type of the disease with extensive nephrotic edema, in which there may be normal blood pressure over a period of years, so that the differentiation from chronic nephrosis is very difficult However, if the blood pressure is measured daily in such patients, transitory rises to 130 or 140 mm. systolic and 90 or 95 mm diastolic pressure in a young adult confined to bed, may reveal the tendency to hypertension. Particularly in children, hypertension is relatively often not demonstrable with certainty Ultimately, even those cases which had ... op hypertension. ... other cachectic ... pressures as 250

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In the recurrent cases, the blood pressure may rise with each exacerbation, to fall to normal between the acute attacks When the disease is of the nephrotic type, the hypertension present during the acute stage may disappear completely, to reappear after months or years, usually as the edema is lessening There is thus a complete change of the clinical picture from one dominated by edema and simulating chronic nephrosis to a complex in which cardiovascular phenomena are the central features and simulating essential hypertension

The hypertension results in left ventricular hypertrophy. For a long period, often many years, the hypertrophied left ventricle may successfully cope with the increased work and there [illegible] of the cardiac borders. However, the signs described in Chapter 26 may demonstrate the existence of hypertrophy of the left ventricle. At times it is remarkable how long the hypertrophied left ventricle continues to meet great arterial hypertension without dilating. There are patients with chronic glomerulonephritis who have a blood pressure as high as 250/140 mm. for several years with little or no enlargement of the cardiac shadow in the teleoroentgenogram. Finally, if the patient is not previously carried off by uremia or some complication, as most frequently happens, the left ventricle gives way and dilates, the left border moving outward. Following this, the right heart also hypertrophies and dilates, as is described in detail in Chapter 26.

Clinically, for years, there is no outspoken evidence of cardiac insufficiency in most cases of chronic glomerulonephritis, the chief danger always being renal insufficiency. But it is probable that in some instances the final diminution in urinary volume which sends the patient with impaired renal function into uremia is due to relative myocardial insufficiency. It is true that in many cases the blood pressure does not drop with the advent of cardiac insufficiency, but in such cases the blood pressure may be maintained in the face of decreased cardiac output only by augmented arteriolar constriction which includes the kidney and diminishes renal blood flow. And the progressive destruction of more renal parenchyma demands an even higher blood pressure than previously to maintain the compensatory polyuria (see below).

There are long-standing cases of chronic glomerulonephritis (secondary contracted kidney) in which the clinical picture of cardiac insufficiency develops. There may be such evidences of left ventricular failure as attacks of pulmonary edema, cardiac asthma, gallop rhythm, and drop in blood pressure. Or if the right heart has also given way, engorgement of the liver, edema of the feet, cyanosis and other evidences of congestive heart failure may appear. It is to be emphasized that such a purely cardiac picture is decidedly unusual in chronic glomerulonephritis, the typical ending is uremia But in the late stages of uremia, heart failure often adds to the misery.

The hypertension may cause other manifestations than those due to its effect on the heart. The headaches so often present in patients with good renal function and no evidence of cerebral arteriosclerosis are doubtless often the result of the hypertension Such headaches may accompany paroxysmal rises in blood pressure, and are probably manifestations of hypertensive encephalopathy. Epistaxis is a common occurrence and may be very profuse. Cerebral hemorrhage is unusual in chronic glomerulonephritis, but does occur, especially in older individuals. Doubtless, cerebral hemorrhage is far rarer in chronic glomerulonephritis than in essential hypertension because patients with the former disease are usually much younger, and their cerebral vessels are not so often markedly atherosclerotic. Occasionally, such angiospastic phenomena as "dead fingers"

A common phenomenon correlated with the hyper-

when the pressure goes down.

Hypertensive Encephalopathy.—Hypertensive encephalopathy may occur but is not as common as in acute glomerulonephritis. It usually appears in the earlier periods of the disease and may recur at intervals over a period of ... and the author. The

Retinal Lesions.—Retinal changes are common in chronic glomerulo-

... retinal lesions was present ...

renal function. Nevertheless, most, although not all, patients with retinal changes ultimately develop renal insufficiency, if it is not present before the retinal lesions appear. The very bad prognostic significance of hypertensive neuro-retinopathy has already been discussed (page 380). Retinal arteriosclerosis and arteriosclerotic retinopathy develop in chronic glomerulonephritis only after hypertension has been present for a number of years, and are not ophthalmoscopically discernible in by any means all such cases. It was mentioned above that chronic glomerulonephritis may first

optic disc.

A slight degree of *exophthalmus* is not rare in severe cases of chronic glomerulonephritis. Barker and Hanes[35] observed exophthalmus in 16 of 33 patients with "chronic nephritis," a much higher incidence than I have noted. They found exophthalmus most often in uremic or suburemic patients. Dr. A. A. Epstein, who called my attention to the phenomenon, has also observed it, especially in cases which are progressing rapidly. Exophthalmus has seemed to me more common in the malignant phase of essential hypertension than in chronic glomerulonephritis. It is often associated with increased intracranial pressure due to edema of the brain.

Impairment of Renal Function and Uremia.—These are the dangers which always confront the patient with chronic glomerulonephritis and which sooner or later terminate the life of most such sufferers. However, in

chemistry is normal. The only sign of the disease at this period may be

The hypertension results in left ventricular hypertrophy. For a long period, often many years, the hypertrophied left ventricle may successfully cope with the increased work, and there is no evidence of dilatation. During this period, the apex beat is within normal limits, and percussion as well as the roentgen picture reveal no lateral displacement of the cardiac borders. However, the signs described in Chapter 26 may demonstrate the existence of hypertrophy of the left ventricle. At times it is remarkable how long the hypertrophied left ventricle continues to meet great arterial hypertension without dilating. There are patients with chronic glomerulonephritis who have a blood pressure as high as 250/140 mm. for several years with little or no enlargement of the cardiac shadow in the teleoroentgenogram. Finally, if the patient is not previously carried off by uremia or some complication, as most frequently happens, the left ventricle gives way and dilates, the left border moving outward. Following this, the right heart also hypertrophies and dilates, as is described in detail in Chapter 26.

Clinically, for years, there is no outspoken evidence of cardiac insufficiency in most cases of chronic glomerulonephritis, the chief danger always being renal insufficiency. But it is probable that in some instances the final diminution in urinary volume which sends the patient with impaired renal function into uremia is due to relative myocardial insufficiency. It is true that in many cases the blood pressure does not drop with the advent of cardiac insufficiency, but in such cases the blood pressure may be maintained in the face of decreased cardiac output only by augmented arteriolar constriction which includes the kidney and diminishes renal blood flow And the progressive destruction of more renal parenchyma demands an even higher blood pressure than previously to maintain the compensatory polyuria (see below).

There are long-standing cases of chronic glomerulonephritis (secondary contracted kidney) in which the clinical picture of cardiac insufficiency develops. There may be such evidences of left ventricular failure as attacks of pulmon
pressure.
edema of t[illegible]
may appear. It is to be emphasized that such a purely cardiac picture is decidedly unusual in chronic glomerulonephritis; the typical ending is uremia But in the late stages of uremia, heart failure often adds to the misery.

The hypertension may cause other manifestations than those due to its effect on the heart. The headaches so often present in patients with good renal function and no evidence of cerebral arteriosclerosis are doubtless often the result of the hypertension Such headaches may accompany paroxysmal rises in blood pressure, and are probably manifestations of hypertensive encephalopathy. Epistaxis is a common occurrence and may be very profuse. Cerebral hemorrhage is unusual in chronic glomerulonephritis, but does occur, especially in older individuals. Doubtless, cerebral hemorrhage is far rarer in chronic glomerulonephritis than in essential hypertension because patients with the former disease are usually much younger, and their cerebral vessels are not so often markedly atherosclerotic. Occasionally, such angiospastic phenomena as "dead fingers"

4 In some patients with old glomerulonephritis, the blood pressure rises to very high levels and the classical picture of malignant hypertension develops—violent *headache*, *hypertensive* retinopathy, and acute depression of renal function with uremia that often progresses rapidly. *Arteriolar* necrosis is found. In these cases the renal failure is due to acute renal arteriolar damage resulting from great diastolic hypertension; the course of events is similar to what occurs in the malignant phase of essential hypertension.

5. Occasionally, drastic salt restriction or the immoderate use of mercurial diuretics seems to precipitate azotemia and uremia. In such cases, the plasma sodium level is low and the nonprotein nitrogen of the blood ma

ne... but such alteration

The impairment of renal function sooner or later leads to ... obvious uremia However, it is common for azotemia to be present for a year or more without subjective symptoms of uremia And there are rare cases of glomerulonephritis in which moderate azotemia (blood urea nitrogen 30 to 50 mg per cent) lasts even three or four years while the patient is still able to work The symptomatology of uremia in chronic ... by other

... glomerulonephritis the functional disturbance is primarily impairment of glomerular filtration However, tubular function is also defective. This may be revealed in patients with long-standing polyuria and hyposthenuria by the excretion of so much water and electrolyte in the urine that dehydration develops They may continue to excrete sodium and chloride in the urine despite plasma levels at which normal kidneys would conserve these ions The dehydration may be immediately obvious from the dry, inelastic skin and dry tongue Dehydration is especially apt to occur if the hyposthenuric patient is on a salt-poor diet or is losing electrolyte and water by vomiting The fundamental cause of the salt and water depletion is prob-

... of

... the

... tubular cells The consequence is that too high a proportion of water and electrolytes escapes reabsorption. As a result of such inadequate conservation of water and electrolytes in chronic glomerulonephritis, dehydration often becomes a prominent and not rarely a dominant feature of the clinical picture The depletion of water and electrolytes reaches its apogee in the cases that have been termed salt-losing nephritis, they are described below

proteinuria. But the danger of renal failure is always present and [illegible]

[illegible]

glomerulonephritis varies immensely from case to case. In some instances renal insufficiency is severe from the start and progresses to fatal uremia within months. In such subacute cases, necropsy generally shows, in addition to severe changes in the walls of and within the loops, "extracapillary" glomerulonephritis with extensive formation of epithelial crescents; there may also be necrosis of afferent arterioles and glomerular loops. In other cases, renal function first becomes significantly impaired only after years or even decades of proteinuria. During this period the patient may succumb to an intercurrent ailment without ever having had azotemia or even hyposthenuria.

Once renal function has been sensibly damaged, the impairment may progress slowly or rapidly. Some patients remain in the compensated stage of impaired renal function for years, while others quickly decompensate.

A patient in the compensated stage of impaired renal function has a daily urinary volume of 2 or 3 liters, or rarely more The specific gravity is low; even during water privation the patient cannot elaborate a concentrated urine. In the most severe impairment, the highest specific gravity that can be attained is 1.010, at which concentration the urine is approximately isotonic with the blood As a result of the polyuria, the patient suffers from nocturia and is thirsty, drinking large quantities of water. Despite the copious ingestion of water, the skin may be dry and inelastic and the patient appear generally dehydrated, presenting an appearance akin to that so often seen in patients with long-standing prostatic obstruction. During the compensated stage, azotemia is absent.

Sooner or later, most patients with compensated impairment of renal function "decompensate," *i. e.*, azotemia and uremic symptoms develop. This occurs under several circumstances:

1. In most long-standing cases of glomerulonephritis, the aggravation of the impairment of renal function sets in insidiously and without evident cause. With no obvious incitant, weakness, anorexia, nausea, vomiting or other uremic symptoms, or anemia, appear and azotemia is discovered. Or a periodic examination of a known nephritic reveals azotemia while he still feels well. In these cases the progression of the uremia is often slow and low grade azotemia may last for years The retina is often negative in these patients. Anatomical examination generally reveals far-advanced hyalinization and extensive obliteration of the glomeruli with atrophy of the appertaining tubules. The arterioles may show hyalinization and the small arteries cellular and fibrous intimal thickening Acute changes in the glomeruli are not prominent and arteriolar necrosis is absent.

2. In other cases, usually of relatively short duration, the renal failure is due to an acute exacerbation of glomerulonephritis with hematuria following a sore throat or other infection Here, the kidneys reveal acute lesions in addition to the long-standing changes.

3. Heart failure sometimes precipitates renal insufficiency in a patient with long-standing hyposthenuria.

go on to coma. The dry and inelastic skin evinces the dehydration. Anemia develops. The blood pressure is normal or low but there is no pigmentation other than perhaps that due to urochrome page 212), which is yellowish and does not involve the mucous membranes. Proteinuria is usually not massive and may be absent for considerable periods. There is hyposthenuria, usually polyuria, azotemia, hyponatremia, hypochloremia, and usually acidosis. Observations by Earle and Murphy and their associates showed that renal blood flow, glomerular filtration, and maximum tubular excretion (PAH) and reabsorption (glucose) are all depressed. Large amounts of sodium are lost in
salt intake is necessary to maintain
learned about the potassium exchange.
was excessive with resultant hypokalemia. In Murphy's patient serum potassium reached as high as 7.4 mEq per liter, except when hypokalemia resulted from massive infusions of sodium salts and dextrose. In Nussbaum's patient the electrocardiogram was indicative of hyperpotassemia. The differential diagnosis from Addison's disease is facilitated by the thera-
rtical hormones,
rnal ketosteroid

The syndrome of salt losing nephritis has been observed to result from

three of the reported cases there were extensive cystic dilatations of the tubules.

The patient can be maintained only by large supplements of sodium chloride If there is acidosis, sodium bicarbonate may also be required.

Nussbaum's patient was maintained for a year after the blood urea nitrogen was 168 mg per cent

The Blood —The non-protein nitrogen shows no abnormalities as long as renal function is unimpaired or such impairment is compensated With the advent of renal decompensation, the characteristic changes in the diffusible constituents occur (page 57)

The proteins and lipids of the plasma are likewise unchanged unless there is copious loss of protein in the urine Proteinuria of sufficient degree to deplete the plasma proteins is generally found in the early stages but may continue for many months or even years in the so-called nephrotic type of glomerulonephritis In such cases the typical nephrotic changes—diminished total protein, inversion of the albumin to globulin ratio, increase in fibrinogen, increase in fat and lipoids—are found These changes in the colloids differ in no wise from those encountered in chronic nephrosis and may be quite as severe as in the latter disease For further details, the reader is referred to Chapter 16 When impairment of renal function supervenes in the nephrotic type of glomerulonephritis, the proteinuria

Individual Renal Functions.—Detailed analysis of individual renal functions by the methods of Homer Smith's school was carried out by Earle[35] *et al.* Similar data have been obtained by Corcoran[36] and his associates, Hilden,[37] Cargill and Hickam,[38] Hogeman,[39] and others. They reveal that renal blood flow, glomerular filtration and tubular function as measured by clearance techniques are all reduced. Until the terminal stage, filtration is reduced more than blood flow (low ratio of inulin to PAH clearance) with the result that the filtration fraction is low. In the late stages the filtration fraction is higher. The predominance of glomerular over tubular damage in the early stages is revealed by the observation of Earle *et al.* that the ratio of the filtration rate to the functional tubular mass (diodrast Tm) is low; later, with progressive tubular damage, this proportion becomes higher. Similarly, Hilden found evidence of predominant glomerular damage in early cases and those in the nephrotic phase, in the form of a low ratio of the urea to the diodrast clearance. Contrariwise, in the terminal stage and in the hypertensive form of the disease, Hilden observed that the urea clearance is high in comparison to that of diodrast. Chasis and Smith[40] demonstrated that in chronic glomerulonephritis with hyposthenuria the proportion of urea which undergoes back-diffusion decreases, with the result that the urea/inulin clearance ratio approaches unity.

By catheterization of the renal vein, Cargill and Hickam found that in chronic glomerulonephritis with decreased renal blood flow, the oxygen consumption of the kidney is decreased, but the extraction percentage is normal.

The question of the functioning of aglomerular tubules in chronic glomerulonephritis has already been discussed (page 609). Inadequate tubular conservation of water and electrolytes in chronic glomerulonephritis with resultant dehydration often becomes a prominent and rarely a dominant feature of the clinical picture. The depletion of water and electrolyte reach their apogee in the rare cases described in the next paragraphs

Salt-Losing Nephritis.—There are very rare cases of renal disease in which salt and water depletion is so severe that the patient goes into a shock-like state Such cases were first described by Thorn[41] and his associates under the name of "salt-losing nephritis" They reported two patients with chronic renal disease (one had chronic glomerulonephritis and the other probably chronic pyelonephritis with extensive cystic change) and normal adrenals in whom the signs and symptoms were indistinguishable from those of acute adrenocortical insufficiency. However, while adrenocortical hormones were of no help, sodium chloride and bicarbonate produced prompt improvement. Since then, cases of such salt-losing
nephritis have be
and tubular calci
Nussbaum[44] *et al.*
and Murphy[48] *et a*
the patient studied
probably also due to chronic pyelonephritis. The cases are usually of insidious onset with a history of such symptoms as weakness, anorexia, emaciation, nausea and vomiting. Mental confusion and drowsiness may

go on to coma. The dry and inelastic skin evinces the dehydration. Anemia develops The blood pressure is normal or low but there is no pigmentation other than perhaps that due to urochrome page 212), which is yellowish and does not involve the mucous membranes. Proteinuria is ... for considerable periods. There is

...

tubular excretion (PAH) and reabsorption ... Large amounts of sodium are lost in the urine with the result that high salt intake is necessary to maintain the patient. More remains to be learned about the potassium exchange. In Earle's case the loss of potassium was excessive with resultant hypokalemia. In Murphy's patient serum potassium reached as high as 7 4 mEq per liter, except when hypokalemia resulted from massive infusions of sodium salts and dextrose. In Nussbaum's patient the electrocardiogram was indicative of hyperpotassemia. The differential diagnosis from Addison's disease is facilitated by the therapeutic response to sodium salts but not to adrenal cortical hormones, normal depression of the eosinophile count by ACTH, normal ketosteroid content of the urine, and normal glucose tolerance curve.

... nephritis has been observed to result from

...

disease starts with and is more pronounced in the tubules ... three of the reported cases there were extensive cystic dilatations of the tubules

The patient can be maintained only by large supplements of sodium chloride If there is acidosis, sodium bicarbonate may also be required.

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diminishes; following this, the blood proteins increase, the albumin to globulin ratio tends to normal, and the lipemia diminishes. Accompanying these changes, the edema diminishes and there occurs the shift in the clinical picture which was mentioned above from one resembling chronic nephrosis to one simulating essential hypertension.

ANEMIA.—Quincke[48] and Hunter[49] long ago pointed out that renal disease may produce anemia. Some patients with chronic glomerulonephritis come to the physician because of pallor or other symptoms of anemia. Anemic symptoms may dominate the clinical picture for a year or more and repeated transfusions may be required to maintain the patient. It has seemed to me that such cases of protracted azotemic anemia have become more common in recent years, perhaps because the life of azotemic patients has been prolonged by better dietary management and more transfusions. The anemia may be very severe Red cell counts below

rough inverse parallelism between the hemoglobin and nonprotein nitrogen of the blood (Ashe,[50] Townsend[51] *et al.*) In the exceptional cases with anemia in the absence of azotemia, the origin of the former is probably other than renal. In some such cases anorexia or dietary restrictions may be concerned, and they may of course abet the azotemic cases. Protein depletion due to proteinuria apparently is not concerned in the genesis of the anemia; in the nephrotic phase without azotemia, anemia is characteristically absent

The anemia is most often normocytic Of 44 patients with azotemic anemia studied by Callen and Limarzi,[52] 34 had normocytic normochromic, 2 microcytic hypochromic, and 8 macrocytic anemia.

The pathogenesis of the anemia is obscure. Characteristic of at least the large majority of the cases is that they are not influenced by the administration of iron, liver, folic acid or vitamin B_{12}. The reticulocyte count is not increased. Nor is the bilirubin content of the serum above normal. Studies of the bone-marrow by Townsend and his associates revealed the latter to be normal or hyperplastic; the hyperplasia was of normoblastic and never of megaloblastic type. Similarly, Callen and Limarzi's studies of the bone marrow in nephrogenic anemia disclosed hypercellular marrow in 80 per cent of the cases. The hypercellularity involved mainly the myeloid cells and megakaryocytes, with normal erythropoiesis They found hypoplasia of the erythroid tissue only when the nonprotein nitrogen of the blood exceeded 150 mg per cent Townsend *et al.* found that while 22 of 27 nephritics without anemia had normal gastric acidity, all of 19 with anemia had diminished acidity after an alcohol meal, 11 of these had anacidity after the alcohol meal and 5 still had anacidity after histamine. They believe that the gastric secretory disturbance plays an important part in producing the anemia through causing a deficiency of "building material" for red cell formation. However, this interpretation does not accord with the occasional finding of ample free acid in patients with azotemic anemia. Callen and Limarzi point out that the development of azotemic anemia in the presence of histologically normal erythroid tissue in the bone marrow indicates defect in the delivery rather than the development of the red

cells. This defect results from renal insufficiency and is correlated with azotemia, but the actual nature of the connection is unknown. On the basis of the survival time of transfused red cells and a variety of other evidence, Loge *et al* [85] conclude that in anemia due to chronic renal insufficiency there is always depression of erythropoiesis, to which is added in some cases an extracorpuscular hemolytic factor.

It has been thought, particularly by French authors (Labbé and Salo- … that the picture of true pernicious

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pernicious anemia

The blood *platelet* count is usually within normal limits even when anemia is severe or when a hemorrhagic diathesis develops The latter is a uremic manifestation and apparently due to capillary damage; not only the platelet count but also the prothrombin concentration are unchanged.

The *white cells* show no constant change in patients with azotemic anemia. Sometimes there is slight leucocytosis with a modest shift to the left in the absence of obvious infection

The Urine.—*Proteinuria* is an almost constant manifestation of chronic glomerulonephritis In cases of very long standing (secondary contracted kidney), the proteinuria is often but slight and rarely even absent during some examinations In the earlier stages of chronic glomerulonephritis the proteinuria is usually very copious This is particularly so in the nephrotic type of the disease, in which a very high degree of proteinuria may be present continuously for months and years In such cases the urinary protein is mostly albumin When impairment of renal function appears, the proteinuria diminishes, the quantity of protein in the urine being a poor prognostic indicator under such circumstances.

diminish in number and become very sparing. It is common when the stage of secondary contract…
find only rare casts
disease are doubly refr…
nephrosis

In the earlier periods of the …re may be sufficient blood in … More often, however, there is only microscopic hematuria. Later in the course, of the disease, the number of red cells present in the urine diminishes, and they are most

… does not establish the diagnosis of chronic nephrosis in a patient presenting a "nephrotic" picture. The presence of large numbers of red cells in the urine is usually indicative of an active inflammatory

process in the glomeruli. If the disease enters the malignant phase (page 614), augmented and even gross hematuria may result from necrosis of renal [illegible]

Gastro-intestinal Symptoms.—Gastro-intestinal symptoms, such as nausea, vomiting and diarrhea are most often uremic manifestations. They may, perhaps, also be due, in patients with general edema, to edema of the mucous membrane of the alimentary tract. However, this often offered explanation has not been proved. In the malignant phase with extreme hypertension, nausea and vomiting may result from edema of the brain. In other cases, however, these symptoms occur in the absence of nitrogen retention, extreme hypertension or edema, their origin being obscure.

Headache.—Headache is a very common and often initial complaint. It may be of uremic nature or else result from the hypertension.

Pains in the Kidney Region.—Pains in the kidney region are decidedly uncommon in chronic glomerulonephritis. However, there are rare instances in which they are severe and protracted (so-called nephritis dolorosa). They usually consist in a dull ache in the lumbar region, but are rarely sharp and radiate to the genitalia and thighs. They have been attributed to swelling of the kidney with stretching of the capsule and to thickening and adhesions of the capsule. Lichtwitz[56] observed such pains in a patient who had a decapsulation during the acute stage, which presumably produced subsequent capsular adhesions.

General Condition.—During long periods, despite the presence of hypertension and proteinuria, the patient may feel relatively well. Such a patient may have no impairment of his working capacity for many years and may even appear ruddy, though more often he is pale But during the active and progressive phases of chronic glomerulonephritis, weakness and anorexia are usually well marked and ultimately, with the advent of uremia, become extreme. During these periods there is usually a waxy pallor which in combination with more or less puffiness of the eye-lids constitutes the "nephritic facies" that often enables one to suspect renal disease at the first glance. With the advent of isosthenuria, the skin is is usually very dry, even in mid-summer, and perspiration is difficult to induce; the hair tends to fall out. When renal insufficiency lasts for a long time, particularly when it is accompanied by protracted vomiting and diarrhea, the emaciation may be frightful, rivalling that seen in cancerous cachexia.

Renal Dwarfism and Renal Osteodystrophy.—Children who have suffered for a long time from renal insufficiency are often retarded in their development. This developmental retardation may be associated with bone deformities and was called renal dwarfism by Barber;[57] other authors use the terms renal infantilism and renal rickets Cases were soon after described in this country by Shipley[58] and his coworkers, Lathrop,[59] Schoenthal and Burpee,[60] and others. Albright[61] and Jaffe[62] and their associates have contributed importantly to understanding of the mechanism of osseous involvement in renal disease.

Some of the cases of gross skeletal disease of renal origin in children are due to glomerulonephritis or pyelonephritis setting in early in life. In a high proportion, however, there is a primary congenital anomaly of the urinary passages with secondary hydronephrotic or pyelonephritic [illegible] Ellis and Evans[63] made the interesting obser-

by hydronephrosis and dilatation of the ureters. Since no obstruction was found, they suggest that the dilatation is due to defective control of the urethro-vesical sphincter. However, since the deficient concentrating ability of these patients leads to marked polyuria over a period of years, it is also possible that the dilatation of the urinary tract is an adaptation of

(known as the Fanconi syndrome) which seems to result from a congenital metabolic anomaly of the renal tubules, one of the manifestations of which is deficient tubular reabsorption of calcium (*cf.* page 32)

The child is usually considerably below the average height, and in adolescent children the secondary sexual characteristics are retarded. The gross skeletal deformities and, as a result of the changes in the epiphyses, the roentgen appearance often resemble those of rickets, although the histological changes are fundamentally different (see below) Knock-knee seems to be the most common deformity and may be very severe. There

were accompanied by marked atrophy of the muscles of the thigh. Such cases have been admitted to orthopedic hospitals because of the deformity without knowledge of the renal lesions and have even been operated upon. The roentgen appearance of the bones, which varies greatly in different cases but often resembles the changes of rickets, is described in detail by

In chronic renal insufficiency in adults, it appears from the detailed

arly occur skeletal

rotic resorption of

ormation." In the

and demonstrable

study. Only very rarely and after many years does renal insufficiency in adults produce osseous changes similar to those just described in children. Albright, Drake and Sulkowitch[65] have published in detail one such case and cite two others; in their patient, the osseous lesions were accompanied by calcium deposits in the neighborhood of joints and medial calcification of the arteries. The osseous changes in

g renal insufficiency have been

has very kindly given me the

"In adults who have suffer

from chronic renal insufficiency, the *bones though* usually not altered grossly, often reveal on microscopic examination mild but clear-cut fibroporotic changes in the spongiosa. *In these cases, the spongy trabeculæ* show scattered resorption lacunæ containing osteoclasts and connective tissue, and some of them may also present, here and there, deposits of new bone. Occasionally—and specifically when the renal insufficiency has been very protracted—*the bones will be found* even grossly altered. In these cases, the spongiosa is close-meshed and the *trabeculæ are thickened and distorted,* so that altogether the condition amounts to an osteosclerosis. The microscopic findings indicate that the ost

time. According to Albright and Reifenstein, the histological changes in renal osteodystrophy are histologically indistinguishable from those in generalized osteitis fibrosa due to primary hyperparathyroidism, but in children they are associated with changes in the epiphyses which do not occur in hyperparathyroidism and in the *x*-ray picture resemble those of true rickets.

While the pathogenesis of the osseous changes due to renal insufficiency

and impairment in renal function. That impairment of renal function favors the development
experiments of Pappenh

due to the calcium deficiency alone. Lyttle[67] pointed out that the gross skeletal deformities occur almost exclusively in those instances of renal disease that set in very early in life, when growth is most rapid and before union of the epiphyses. The bony lesions apparently occur only in children with long-standing impairment of renal function as demonstrated by inability to elaborate urine of normally high concentration. Sooner or later the impairment of renal function becomes decompensated, nitrogen retention appears, and the child ultimately succumbs to uremia. Histological studies (*cf.* Albright[65] *et al* and Shelling and Remsen[68]) indicate that the changes in the bones are fundamentally the same as those present in primary parathyroid adenoma and those which were produced by Jaffe[69] and his coworkers by the continuous administration of parathyroid extract—conditions in which hyperparathyroidism leads to excessive mobilization of calcium from the skeleton. The problem of the pathogenesis of renal osteodystrophy is thus really that of the mechanism by which renal insufficiency leads to the removal of excessive quantities of calcium from the skeleton. Several factors may be involved:

1. The ability of the insufficient kidney to form a highly acid urine and to synthesize ammonia is decreased page 45). In consequence of inadequate urinary acidity and ammonia formation, the organism is compelled to excrete fixed base in order that the acid end-products of metabolism may be eliminated. Among the fixed base on which the organism

draws is that stored in the bones and there thus results decalcification

tion of the mineral from the bones. ... a result of the deficient renal excretion of phosphate, more of this ion is eliminated into the intestine and there interferes with the absorption of calcium through the formation of insoluble calcium phosphates, thereby favoring calcium deficiency and consequent skeletal changes

Both glomerular insufficiency (retention of phosphate and other anions) and tubular failure (inadequate reabsorption of calcium and other kations) may thus participate in the genesis of the skeletal changes; their relative importance varies in different types of renal disease (*cf.* Albright and Reifenstein[72])

Evidence has been accumulated which indicates that, whatever the precise mechanism through which renal insufficiency produces the osseous

mentioned case of Albright, the parathyroids weighed no less than 11 grams Albright and his associates have advanced the hypothesis that the stimulus to the hyperplasia of the parathyroids is phosphate retention;

trophy with ordinary rickets As the latter investigator points out, the action of irradiated ergosterol in promoting absorption and storage of calcium and phosphorus is not confined to rickets. Much more often, antirachitic therapy has little or no effect on the osteodystrophy (Hess[78] and others, one personal observation), certainly nothing like the effect that one anticipates in banal rickets As mentioned above, the histological changes in renal osteodystrophy are much more closely related to those of hyperparathyroidism than to those of rickets, and the term renal rickets is a misnomer.

DIAGNOSIS OF CHRONIC GLOMERULONEPHRITIS

As a rule, the recognition of chronic glomerulonephritis presents little difficulty. In typical cases, the proteinuria, hematuria, impairment of renal function, edema, hypertension, etc. constitute an unequivocal picture. The diagnosis is easier when there is a history of acute glomerulonephritis, but this is absent even more often than is a history of rheumatic fever in middle-aged women with mitral stenosis. In cases in which the history of acute glomerulonephritis is wanting, and in which only one or two of the just-mentioned manifestations are present, the diagnosis may be difficult or impossible for a long time, sometimes until the post-mortem examination.

In children with proteinuria in the absence of other evidences of renal disease, the question often arises whether the coagulable urine manifests *orthostatic proteinuria* or is due to chronic glomerulonephritis (*cf.* page 401).

A frequent dilemma is whether a nephrotic syndrome results from *chronic (lipoid) nephrosis* or glomerulonephritis. For the many who do not believe that chronic nephrosis exists as an independent entity, the problem does not exist, and at present from a strictly pragmatic point of view it is not of much importance. In Chapter 16, however, evidence is presented that chronic nephrosis is a nosologic entity and its characteristics are described.

Differentiation between chronic *pyelonephritis* and glomerulonephritis may be difficult or even impossible. In the past, most cases of pyelone-
phritis were mistakenl
At present, at least in
of the two disorders
pyelonephritis which first come under observation when they have hyper-
tension and/or renal
result from pyelonep
may produce the clin
tensive retinopathy.
speaks for pyelonephritis, apart from rare instances of complication of glomerulonephritis by a urinary tract infection. But it must be remembered that in long-standing chronic pyelonephritis, when the infection is quiescent or abolished, and especially when antibiotics have been given, the urine may contain very few white cells. And in active glomerulonephritis, considerable numbers of polymorphonuclear leucocytes are present in the sediment, though there are no clumps. A few red cells are not unusual in the centrifuged sediment in pyelonephritis, but marked hematuria is rare; it may result from hemorrhagic cystitis. While during most of the course of chronic pyelonephritis the sediment contains few casts, in the terminal uremic stages, large granular and waxy casts may be abundant (Lippman,[79] own observations) There are cases of chronic pyelonephritis with marked proteinuria, but it is never as massive as in the nephrotic stage of glomerulonephritis. The urine is sterile in glomerulonephritis, while organisms can often be demonstrated in the stained sediment or by culture in chronic pyelonephritis. But in many cases of long-standing pyelonephritis organisms can not be found. Edema occurs only in the late stages of pyelonephritis, is usually slight, and is almost always of cardiac

Fever and chills may be due to chronic pyelonephritis; not rarely ... of obscure pyrexia. ... result of a complica- ... onephritis (page 649).

In many cases, the history of either acute glomerulonephritis or acute ... clarifies the state of affairs. ... (especially during pregnancy) ...

... to believe that the ... diabetic the appearance of proteinuria or ...

There are cases of chronic glomerulonephritis in which hypertension is associated with only slight proteinuria and but little impairment of renal function. When such a case occurs in an individual past youth, and there is no history of acute glomerulonephritis or edema, the differentiation from *essential hypertension* may be difficult or impossible. Actually, in some such cases that I have seen the family history and sthenic bodily habitus indicated that the glomerulonephritis had affected an individual with the hereditary basis of essential hypertension. The sometimes difficult or impossible differentiation between chronic glomerulonephritis and the malignant phase of essential hypertension is discussed on page 835.

In tuberculosis and other long-standing suppurations, the question formerly arose quite often, and still does on rare occasions, whether *proteinuria* is due to *amyloidosis* or chronic glomerulonephritis, which in such ...

by the Congo red test or biopsy (page 525). Any considerable hematuria speaks for glomerulonephritis, unless it is due to tuberculosis of the kidney. It should be remembered that glomerulonephritis is rare in suppurative tuberculosis, while amyloidosis was until recently very common and still is not a rarity. Most of the erroneous diagnoses that I have seen have consisted in mistaking amyloidosis for glomerulonephritis and not the reverse.

Polycystic kidneys may present a clinical picture akin to that of glomerulonephritis with *hypertension*, cardiac hypertrophy, hematuria and renal insufficiency; palpation or radiography of the enlarged kidneys will usually reveal them.

Periarteritis nodosa or the *wire-loop lesions of disseminated lupus erythematosus* (page 537) are not rarely difficult to differentiate from chronic glomerulonephritis. Since the urinary changes in periarteritis and disseminated lupus may completely mimic those of glomerulonephritis, recognition of the two former diseases depends on demonstration of their *positive characteristics*. Marked hypertension is very rare in disseminated lupus. In recent years, demonstration of the L.-E. cell has been a great help in the recognition of disseminated lupus.

PROGNOSIS OF CHRONIC GLOMERULONEPHRITIS

Prognosis in chronic glomerulonephritis resolves itself into two main questions: (1) The possibility of complete recovery; and (2) the probable expectation of life.

The severity of the initial acute attack is not always an accurate index of the subsequent course, severe acute attacks may be followed by complete recovery within a few months, while cases setting in insidiously may develop into severe chronic glomerulonephritis which proves fatal within months or a few years.

During the first year after the onset of glomerulonephritis, recovery is *possible* even in extremely severe cases However, when there is continued impairment of renal function and hypertension increases, recovery is improbable after even a few months. In general, those cases in which edema is the outstanding manifestation during the first months have a better chance for recovery or at least a protracted course than those in which hypertension persists for as much as two months It is the cases in which hypertension lasts for more than a few weeks that tend to rapid deterioration of renal function, hypertension after the first weeks is of ill prognostic omen. After glomerulonephritis is present for more than a year, no matter how mild its manifestations, complete recovery is very dubious, and this scarcely occurs after two years An exception is possibly constituted by those cases which remain with only proteinuria but no impairment of renal function, hypertension or edema following the acute attack; some such residual proteinurias persist for decades without developing other evidences of chronic glomerulonephritis. It is possible that in some of these cases the proteinuria ultimately disappears. But in others after twenty years or more of nothing but proteinuria, impairment of renal function and hypertension appear, and the patient succumbs to uremia

By far the most important single factor in determining the duration of life in glomerulonephritis is the rate at which deterioration of renal function progresses. The tempo of the process varies greatly from case to case. In rare instances, the fatal impairment of renal function with uremia develops within weeks, in another group it takes months, while in still others renal failure occurs only after decades. I have seen cases in which the duration of chronic glomerulonephritis ultimately terminating in uremia was over thirty years.

... of injury to the kidney usually cannot be estimated ... period ... rating. ... ing the ... most useful ... the specific gravity test. In pro- ... crease in the maximum attainable specific gravity of the urine is noted, although, as a rule, the downward progress is not continuous. After isosthenuria (maximum specific gravity about 1 010) is reached, the specific gravity is no longer of help and the state of renal function is best judged by the blood urea nitrogen and urea clearance.

Some patients with hyposthenuria due to chronic glomerulonephritis retain their working capacity for years, even ten or more. The same is true of those with moderate hypertension or recurrent slight edema. However, such individuals are always in danger Among the causes of aggravation of previously impaired renal function are intercurrent infections of the throat and respiratory tract, although this danger is not as great as before antibiotics, and pregnancy The woman with chronic glomerulonephritis becomes pregnant only with much risk (*cf.* Chapter 32) In the cases in which hypertension is present for years without great impairment of renal function, death from cardiac failure or an independent cause may terminate the disease before its "natural" ending, which is

...

malignant phase with hypertensive retinopathy and rapidly progressive renal insufficiency is usually not more than a year or two away.

The appearance of hypertensive retinopathy is of very bad prognostic significance, the patient usually succumbs in less than two years advent of

...

encephalopathy due to edema of the brain.

Epileptiform convulsions and other manifestations of hypertensive encephalopathy are of much graver prognostic significance in chronic than in acute glomerulonephritis Death may occur during the seizure or within a relatively short period thereafter However, this is not always true, as illustrated by the patient studied by Oppenheimer[32] and the writer, who had dozens of severe convulsive seizures during a period of three years

Patients with the nephrotic type of chronic glomerulonephritic usually do not survive more than a year or two after the appearance of edema. However, there are exceptions who get along for several years, and these, from present indications, are more common since ACTH and cortisone have been used in the treatment of the nephrotic syndrome I have not seen any instance of the nephrotic syndrome which the history or other evidence indicated clearly to be due to chronic glomerulonephritis in which

Once renal decompensation with nitrogen retention in the blood appears in chronic glomerulonephritis, only a minority of the patients survive more than two years. However, in exceptional cases, especially with careful dietetic management, the patient may get along quite well and with some working capacity for several years. The prognosis is, of course, worse if nitrogen retention appears while the patient is on a low-protein diet than if it is found when the diet has been unrestricted. There are unusual cases of outspokenly recurrent type, in which azotemia accompanies the acute exacerbations, to disappear with their subsidence. Also, although this is uncommon in chronic glomerulonephritis, nitrogen retention due to a combination of impaired renal function and well-marked cardiac failure may clear up on bed-rest and other treatment for cardiac insufficiency.

When well-marked uremic symptoms—nausea, vomiting, diarrhea, mental torpor, delirium, uremic eruptions, pericarditis, etc.—appear, it is rare for the patient to improve even temporarily. But even here surprises occur; on rare occasions, even patients with uremic pericarditis improve enough to leave the hospital, although the respite proves only temporary.

TREATMENT OF CHRONIC GLOMERULONEPHRITIS

Treatment during the first year of glomerulonephritis has already been outlined. The treatment of acute exacerbations of chronic glomerulonephritis does not differ essentially from that of the initial attack except that bed rest is often not enforced for as long a period in the effort to favor complete *restitutio ad integrum*, which at this stage is highly improbable or impossible.

The Diet.—Opposing indications often conflict with one another in the selection of the diet in chronic glomerulonephritis. Excretory insufficiency calls for protein restriction, while massive proteinuria and the nephrotic syndrome indicate an ample protein intake. The difficulties arise when both these indications co-exist in the same patient.

Little dietary restriction is called for in the asymptomatic stages of chronic glomerulonephritis with no edema, modest proteinuria, good excretory function, normal plasma proteins and at most slight hypertension. There is no evidence that in such cases restriction of protein slows the progress of the renal lesions, or that such effect as very rigid salt restriction may have on the blood pressure (less will certainly have no effect) is worth the requisite interference with the patient's way of life. The asymptomatic stage of chronic glomerulonephritis often lasts for several years and may endure for decades; the evidence is lacking to justify the imposition of permanent dietary invalidism on such individuals, who feel well, contribute useful activity and enjoy life. The writer not rarely encounters patients who have been put on stringent diets merely because proteinuria has been found in an insurance examination. It will be seen (Chapter 25) that there is no convincing evidence that the end-products derived from the usual amount of protein in the diet in any way injure the kidney or accelerate the downward course or renal damage already present. Keutmann and McCann[80] fed 4 patients with chronic glomerulonephritis with hematuria between 40 and 200 grams of protein daily over a protracted period;

hematuria diminished, renal function improved, and the general condition ... period of the liberal protein ration.

why especially large quantities of protein should be eaten. ... people can get along with a daily ration of 1 gram of protein per kilogram body weight. A diet containing this amount of protein can be made palatable over years even for individuals who have always been "meat eaters." Many patients with chronic glomerulonephritis have been so ... fear of meat and other protein foods that it is difficult

patients with chronic glomerulonephritis who have been kept on an inadequate ration of protein for a long time despite good renal function, to observe improvement in bodily vigor and anemia quickly after the institution of a diet containing adequate nitrogenous foods. In some such cases, notably those with hypertension and proteinuria but tolerably good excretory function the fear of the patient for protein foods other than milk

impairment of excretory function The protein intake should than be restricted and every effort made to keep endogenous protein breakdown as low as possible by a high carbohydrate and fat intake. Further details of the low protein, high calory diet will be found in Chapter 7

An indication for considerable quantities of protein in the diet is furnished by the nephrotic type of glomerulonephritis, *i e*, the type of case with massive proteinuria, tendency to edema, tolerably good excretory function and usually but moderate or no hypertension. In such cases, sufficient protein should be given to cover the loss of protein in the urine as well as the metabolic requirements, and in addition to repair the protein starvation which has usually developed before the start of dietetic treatment. Under such circumstances the requisite daily protein ration for at least a period of weeks or even months may be over 100 grams Such a diet is not uncommonly followed by lessening or even disappearance of edema But before giving so much protein one must be sure that ... patient should be able to concentrate ... 1 020 and the blood urea should be ... the technique of the high protein diet

Fluid intake is to be regulated in accord with the functional capacity of the kidney ...

aided by the spontaneous thirst of hyposthenuric patients. In such cases with azotemia, increase in fluid intake often results in decrease in

blood urea. Unless the patient has been previously dehydrated, or the weather is very hot, nothing is to be gained by increasing the water allowance above 2500 or 3000 cc. daily. Heart failure is not a contra-indication to raising the fluid allowance.

Sodium [illegible]
in whom n [illegible]
fluid reten [illegible]

[illegible] danger of sodium depletion, though even here it must be watched for. But when there is hyposthenuria with or without azotemia, sodium restriction is to be carried out only with much circumspection because of the danger of salt depletion. If the syndrome of "salt-losing nephritis" (page 6[illegible] [illegible] rare in glomerulo-

[illegible], contrary to those [illegible]-Wilson syndrome or essential hypertension, to become obese. But if obesity (not edema) does appear on the low protein, high calory diet, the caloric intake should be lowered.

Medicinal Treatment.—No medicinal agents have been demonstrated to alleviate or retard the progress of the lesions in the kidneys. There is no [illegible], antibiotics, cortisone or ACTH specifically

[illegible] that ACTH and cortisone have not been shown to alter the progression of the glomerular lesions, they have proved the most valuable therapeutic agents available in many instances of the nephrotic syndrome due to chronic glomerulonephritis. The cases in which they are most apt to prove of help are those in which the nephrotic syndrome occurs in the presence of tolerably good excretory function, normal blood urea and little or no hypertension. In such instances of the nephrotic type of chronic glomerulonephritis, ACTH and cortisone may produce results similar to those obtained in chronic nephrosis: diuresis, evacuation of edema, repair of hypoalbuminemia and decrease in lipemia (*cf.* Chapter 16). However, worthwhile results from ACTH and cortisone are not as frequent in the nephrotic form of glomerulonephritis as in chronic nephrosis, and they are usually even more transitory. When the nephrotic syndrome is accompanied by azotemia or marked hypertension, significant diuresis is even less frequent, and untoward and even dangerous side effects are not as rare. I have several times seen aggravation of hypertension by ACTH and once threatening pulmonary edema developed. Azotemia may be markedly aggravated. For these reasons, I have not recently used ACTH or cortisone for the treatment of chronic glomerulonephritis when there is azotemia or more than minimal hypertension. Details of the administration of ACTH and cortisone will be found on page 490.

Diuretics have a limited sphere of usefulness in chronic glomerulonephritis and are rarely long continued. Theophyllin and other xanthines alone are valueless. Urea or ammonium chloride sometimes produce modest diuresis, but it is rarely significant; these diuretics should not be used if excretory function is impaired, and they are rarely long continued.

Exceptionally, mercurials produce profuse diuresis, but more often they fail, and of there is initial success the good result is rarely repeated many times. The mercurials should not be used when there is hematuria or marked

effects. Salt-poor albumin will often produce ... proves worth the considerable expense. Further details regarding these

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have

administered the drug to patients with chronic glomerulonephritis (2 doses of 0.2 mg/kg, on successive or alternate days). In some of the patients, diuresis occurred, edema was evacuated, proteinuria diminished and the filtration rate increased. Kelley and Panos[57] obtained diuresis with nitrogen mustard in 8 of 9 children with the nephrotic syndrome, but there was no consistent effect on proteinuria. Apparently, the results of treatment with nitrogen mustard, with which the writer has insignificant personal experience, are usually temporary. Because of the possible side effects of nitrogen mustard, its use is to be regarded as still in an investigative stage.

In many cases of chronic glomerulonephritis *anemia* becomes a prominent or even the dominant manifestation for months or even years. The anemia may appear with only modest azotemia, *e.g.*, 50 mg. urea nitrogen per 100 cc blood. Unfortunately, the characteristic normochromic

lar failure in these usually hypertensive individuals. In some patients with chronic glomerulonephritis protracted protein restriction contributes to the genesis of edema, in these, increase in the protein ration may be of help. If there are no symptoms of clearly anemic origin, transfusions should not be started in chronic glomerulonephritis unless the hemoglobin falls below 9 grams. Some patients require 25 or more transfusions over a period of a year or two.

If heart failure develops, digitalis is called for. Feil and Steuer[82] found that the amount of digitalis necessary to produce clinical and electrocardiographic evidences of digitalization or symptoms of intoxication is not lessened by renal insufficiency. However, since it has been possible to gauge dosage somewhat more accurately by the use of pure glycosides, it has seemed to me that the maintenance dose of digitalis preparations is less in the presence of renal damage severe enough to produce even slight azotemia. This is hardly surprising, Okita[83] *et al.* have shown that 60 to 80 per cent ...

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because it may

... to decide whether nausea and vomiting are due to overdosage or uremia. In the prescription of salt restriction and mercurial diuretics

blood urea. Unless the patient has been previously dehydrated, or the weather is very hot, nothing is to be gained by increasing the water allowance above 2500 or 3000 cc. daily. Heart failure is not a contra-indication to raising the fluid allowance.

Sodium restriction is indicated in patients with edema, as well as in those in whom massive proteinuria and/or hypoproteinemia indicate liability to fluid retention. Marked hypertension also calls for sodium restriction. In patients with the nephrotic form of glomerulonephritis, tubular function is usually adequate to permit dietary sodium restriction to levels as low as 500 mg. per day without great danger of sodium depletion, though even here it must be watched for. But when there is hyposthenuria with or without azotemia, sodium restriction is to be carried out only with much circumspection because of the danger of salt depletion. If the syndrome of "salt-losing nephritis" (page 622) appears, which is rare in glomerulonephritis, a high salt ration may be used.

It is rare for patients with chronic glomerulonephritis, contrary to those with the Kimmelstiel-Wilson syndrome or essential hypertension, to become obese. But if obesity (not edema) does appear on the low protein, high calory diet, the caloric intake should be lowered

Medicinal Treatment.—No medicinal agents have been demonstrated to alleviate or retard the progress of the lesions in the kidneys. There is no evidence that antihistaminics, antibiotics, cortisone or ACTH specifically affects glomerulitis.

Notwithstanding the fact that ACTH and cortisone have not been shown to alter the progression of the glomerular lesions, they have proved the most valuable therapeutic agents available in many instances of the nephrotic syndrome due to chronic glomerulonephritis. The cases in which they are most apt to prove of help are those in which the nephrotic syndrome occurs in the presence of tolerably good excretory function, normal blood urea and little or no hypertension. In such instances of the nephrotic type of chronic glomerulonephritis, ACTH and cortisone may produce results similar to those obtained in chronic nephrosis: diuresis, evacuation of edema, repair of hypoalbuminemia and decrease in lipemia (*cf.* Chapter 16) However, worthwhile results from ACTH and cortisone are not as frequent in the nephrotic form of glomerulonephritis as in chronic nephrosis, and they are usually even more transitory. When the nephrotic syndrome is accompanied by azotemia or marked hypertension, significant diuresis is even less frequent, and untoward and even dangerous side effects are not as rare. I have several times seen aggravation of hypertension by ACTH and once threatening pulmonary edema developed. Azotemia may be markedly aggravated. For these reasons, I have not recently used ACTH or cortisone for the treatment of chronic glomerulonephritis when there is azotemia or more than minimal hypertension Details of the administration of ACTH and cortisone will be foun

Diuretics have a limited sphere of

nephritis and are rarely long continued.

alone are valueless. Urea or ammonium chloride sometimes produce modest diuresis, but it is rarely significant; these diuretics should not be used if excretory function is impaired, and they are rarely long continued.

Sufferers from glomerulonephritis who are ambulatory should be particularly careful to avoid contact with individuals having a sore throat or other infection. Every effort should be made to avoid exposure to inclement weather because of the danger of sore throat, etc.

There is no objection to the use in moderation of alcohol, tobacco, coffee ... ure in essential

even slight peripheral edema.

Moderate exercise, preferably walking or not too much golf when the weather is good, should be encouraged in patients whose cardiac reserve is adequate. Strenuous exertion is to be avoided; even healthy people often have protein and sometimes red cells in the urine after violent exertion. ... ren, although ... Sea-bathing ... dicted in patients with any evidences of activity of the nephritic process; it will be recalled that red cells are often found in the urine after sea-bathing However, basking in the sun on the beach is to be encouraged.

An occupation is preferable, if at all possible, which does not involve hard physical work or exposure to cold and wet The question of future occupation often arises in youths with proteinuria but no other manifestations, and may be difficult to decide Positions in offices or as salesmen or teachers are examples of well-suited occupations. One must never give advice regarding occupation which it is economically impossible for the patient to follow, psychologic trauma is then added to the physical difficulties.

containing waters, which is often part of the regimen, may be distinctly harmful

The question often arises whether an individual in an asymptomatic stage of chronic glomerulonephritis should permanently change his residence to, or enter college in, a warm climate Careful consideration should be given to economic and social factors before giving advice in this regard.

It is important that climatic treatment should not be suggested to an individual who cannot afford it, the benefits to be anticipated are not sufficient to warrant the great financial sacrifices which such patients sometimes make to attain them.

for heart failure in glomerulonephritis, the state of renal function must be borne in mind so as to avoid the danger of salt depletion.

Treatment of Infectious Foci.—Patients with glomerulonephritis should be examined for infectious foci. If an infection is found and may be helped by an antibiotic, it should be given. Should infected tonsils, teeth or sinuses be found which would require surgical treatment in the absence of glomerulonephritis, this should be done. In general, it is well to postpone operative intervention until acute manifestations have cleared up, for tonsillectomy and other operations on infected foci are occasionally followed by exacerbation of symptoms. Thus, Page and Alving[84] found, by means of [illegible] was depressed in the days immedi- [illegible] nephritics who underwent removal [illegible] ed case, uremic symptoms were precipitated. There was also often increase in hematuria and cylindruria for some days after operation. As a rule, little or no benefit is seen after such procedures, and one should be careful not to exalt unduly the hopes of the patient or his family with regard to the results of removal of tonsils or teeth. Observations of improvement of the nephrotic syndrome in children following surgical or other drainage of an infected paranasal sinus have been mentioned (page 454), but I have not had similar good fortune There can be little doubt that "removal of foci" was long overdone; particularly the puncture of sinuses has been carried out too often It is rarely necessary since the introduction of penicillin. I am not sure that I have seen improvement in glomerulonephritis unequivocally due to surgical treatment of an infected focus

Physiotherapy.—Sweating procedures and various types of baths are often used in glomerulonephritis, particularly in European spas. Bronner and Schueller[85] advocated diathermy in "chronic nephritis." There is no reason to think that any of these procedures help other than through suggestion.

Surgical Treatment.—Edebohls[86] and others claimed improvement and even cure of chronic glomerulonephritis from decapsulation. Such an operation comes into consideration only during acute exacerbations with extreme oliguria or anuria, and the remarks made in the chapter on Acute Glomerulonephritis apply equally to the acute phases of the chronic disease. I have never recommended the operation in chronic glomerulonephritis

General Management.—Patients who feel well enough to be up and about should be allowed to do so unless they have heart failure, are in an acute exacerbation with hematuria, or have an intercurrent infection. Edematous patients seem to do about as well when up and about as when bed rest is enforced; moderate increase in the edema of the legs as a result of leaving bed is not harmful. The same is true of such symptoms as proteinuria, the presence of small or moderate numbers of red cells in the sediment, hypertension and impairment of renal function, if they seem to be stationary, the patient may be allowed to get about. Many patients carry on an occupation for years despite slight edema that comes and goes, proteinuria and microscopic hematuria.

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many of the cryptogeni

predominance In Nesbit and Cooper's

There may be a

ion, for Perkoff[10]

ers were affected

The colon bacillus is the organism most often cultured from the urine, but there are also many cases due to aerobic and anaerobic streptococci, staphylococci, Aerobacter aerogenes, proteus, pyocyaneus and other bacteria. In the obstructive cases mixed infections are common Wilhelm's[11] detailed studies of the bacteriology of chronic pyelonephritis have revealed that,

mon He found that Aerobacter aerogenes has been especially frequent and there is also a considerable incidence of pyocyaneus infections. In interpreting urinary cultures, especially for the differential diagnosis between pyelonephritis and glomerulonephritis, it should be borne in mind that bladder urine from healthy persons may reveal organisms (Schulte,[12] Slotkin[13]) Schulte found that urine obtained from the bladder through the cystoscope often affords positive cultures, but this is not true of the renal pelvis.

Pathological Anatomy.—The disease may be bilateral or, a little less often, unilateral In the kidney involved by chronic pyelonephritis one almost invariably encounters an admixture of acute and chronic inflammatory processes and the scarring in which healing terminates; in very long-standing cases evidences of active inflammation may be scanty. Most

the two kidneys are usually much more pronounced than in glomerulonephritis and there are completely unilateral cases Sometimes the diagnosis of chronic pyelonephritis can be made with confidence from the gross appearance, but often differentiation from glomerulonephritis, the arteriolosclerotic kidney or multiple, healed infarcts requires microscopic examination. The kidneys vary in size from normal or even slightly enlarged to extremely small organs. One kidney may be so small that such an organ has been confused with congenital hypoplasia (*cf* Emmett[12] *et al*). The

Chapter

22

CHRONIC PYELONEPHRITIS

Only in the past two decades has the profession become cognizant of the great frequency and importance of chronic pyelonephritis. Indeed, if both the acute and chronic stages of pyelonephritis are included, it is doubtless much the most frequent of kidney diseases Of 93 cases with uremia coming to necropsy, 32 were due to pyelonephritis (Likely[1] *et al.*). At necropsy one very often sees scars in the kidneys which are due to healed pyelonephritis, although there is no history of the disease. For many years the acute illness characterized by pyuria, fever and chills was diagnosed as "acute pyelitis," but the studies of Wilson [illegible] and others showed that they are [illegible] anatomy was described many y[illegible]lein,[4] and urologists have long been familiar with the renal changes secondary to obstruction and infection of the urinary passages. However it is only since the publicat[illegible] have appreciated [illegible] of the lower urinary tract, chronic bacterial infections of the kidneys produce clinical pictures characterized by impairment of renal function and hypertension, and frequently terminating in uremia. There can be no doubt that in the past many cases of pyelonephritis have passed for glomernephritis At present, in New York City at least [illegible] the [illegible] tissue of the kid[illegible] uli is secondary. In a high proportion of the cases the renal point of departure is obviously the pelvis; how many take origin in the intertubular tissue of the kidney remains to be demonstrat[illegible] may well be the [illegible] each the kidney [illegible] d stream; while [illegible], it has not been established.

Etiology and Pathogenesis.—There are two great groups of cases: Those in which pyelonephritis is secondary to infection or obstruction of the urinary passages, and those in which neither clinically nor anatomically is the source of the renal infection demonstrable and there is every reason to believe that the bacteria reached the kidneys via the blood stream.



Fig 34 – Section of the kidney of Fig 33, under the low power the dilated tubules containing casts look like thyroid tissue

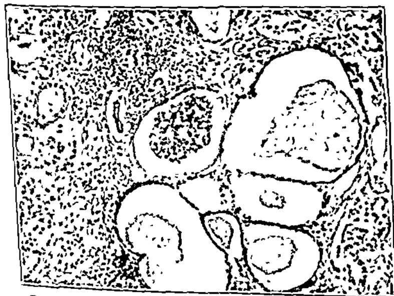


Fig 35 —Higher power of 33 showing dilated tubules, interstitial cellular infiltration and a thickened small artery

capsule is often thickened and strips with difficulty, taking with it bits of kidney tissue. The surface of the kidney is usually irregularly pitted and granulated with depressed scars and nodular elevations composed of normal or hyperplastic tissue. The granulation is generally much more uneven than that of glomerulonephritis or arteriolosclerosis. Rather broad and shallow depressions are common. On section the cortex is irregularly narrowed in the cases with [illegible] on of the process is evident in the cut s [illegible], covered with exudate, or pearly-white and thickened, depending on the stage of the process at th [illegible] there was urinary obstruction, it is [illegible] vis and calyces. However, in most [illegible] the urinary tract, and presumably of hematogenous origin, the pelvis is not enlarged and may

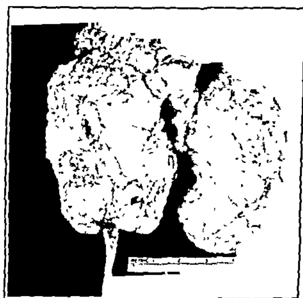


FIG 33 —Chronic pyelonephritis of about five years' duration with continuous pyuria, recurrent febrile episodes and final uremia There were no changes in the urinary passages

be much shrunken. In cases which have succumbed during an acute exacerbation, abscesses may be present.

Histologically, a variegated picture is seen, which usually is the resultant of repeated episodes of interstitial inflammation and healing. Except with extreme contraction, the process is patchy. Most striking at first glance are usually extensive cellular infiltrations and areas of dilated tubules containing large casts and lined by flattened epithelium. Tiny vestiges of atrophic tubules are interspersed. The interstitial infiltrates are usually composed almost entirely of lymphocytes and plasma cells, but large numbers of polymorphonuclear leucocytes may bear witness to an acute exacerbation. The tubules may then contain pus. Areas of fibrous connective tissue are present in long-standing cases. Periglomerular fibrosis is often prominent and a smaller or larger proportion of the tufts shows

hypertension. In many instances of pyelonephritis with profuse pyuria, the sediment contain ... no red cells or casts. But episodes of gross hematuria ma ... whether the blood ... renal insufficiency, ... Proteinuria varies greatly. Usually, the urine does not contain more ... be several

... In the pyelonephritic contracted kidney, as well as ... the inflammatory process is quiescent, proteinuria may be minimal and even absent at times

Bacteria may be demonstrable in the urine by culture and stainable in the sediment. B coli is the most common organism but a large variety of others may be found and there may be mixed infection For long periods ... not be demonstrable despite the presence of pus in the urine.

... are present in the urine it is usually acid, while proteus infections may result in alkaline urine. Longcope pointed out that with renal insufficiency

... becomes sensibly impaired. However, sooner or later this generally occurs and is documented by hyposthenuria, decreased urea clearance and phenolsulphonphthalein excretion, and ultimately azotemia Often the disease is not detected until the patient is uremic, she may state that she felt well until a short time before The progress of the renal insufficiency is often remarkably slow, almost as slow as in polycystic disease, patients may have azotemia for more than five years and yet be active Deterioration and improvement in renal function may be correlated with appearance

... function disproportionately more severe than the damage to glomerular filtration, he observed in many cases that diodrast Tm is depressed more than is inulin clearance The excellent study of Nussbaum[14] and his as-

... number of such "nephrotic syndromes" I have seen in prostatics is too large to be fortuitous

varying stages of hyalinization, fibrosis and atrophy. Individual glomeruli may be the site of a glomerulitis indicated by increase in the number of nuclei. Almost always, however, there are some normal glomeruli. The small arteries in involved areas are often the seat of endarteritis similar to that seen in glomerulonephritis (page 601). Hyalinization of the afferent arterioles may be present. If the hypertension has entered the malignant phase, arteriolar necrosis may be present and with it necrotic glomeruli. The wall of the pelvis is usually thickened and the site of cellular infiltration. The capsule likewise shows perinephritis.

Clinical Picture.—When chronic pyelonephritis complicates urolithiasis, prostatism, neurogenic bladder or another lesion of the urinary tract which is still present, the clinical picture is a composite of the symptomatology emanating from the original and the renal affection. In other cases there is a history of acute pyelonephritis during childhood or during pregnancy or of lower urinary tract disease, but this was followed by a period of years during which the patient regarded herself as well or may have known of asymptomatic pyuria. In still other cases, and these are the ones which come most often initially in the purview of the internist, the disease apparently arises *de novo* with no evidence to show whether it resulted from hematogenous or ascending infection. Some of the patients have a long history of weakness, inability to gain weight, "anemia" which may be real or merely a sallow complexion, "albumin in the urine," recurrent fever and chills regarded as colds, backache, abdominal pains (cases of pyelonephritis have undergone laparotomy), or other symptomatology, the relationship of which to pyelonephritis passed undetected. There may have been recurrences of pyelonephritis during successive pregnancies with complete well-being in the intervals. Some of the patients have been known to have pyuria for years but have felt entirely well It is not very rare for the patient first to come under clinical observation when already uremic; in such cases the urine may contain only a few white cells and the case may be interpreted as glomerulonephritis until the post-mortem examination Formerly, there were cases of pyelonephritis which went continuously downhill and succumbed to renal insufficiency in less than a year, but these hardly occur now with the improvement in antibacterial therapy.

Fever and *chills* are present in the history of many of the patients. Usually these have been regarded as colds. Low grade fever may persist for months, sometimes with exacerbations of higher pyrexia of septic type. In other cases, however, there is no history of febrile episodes and the temperature is not significantly elevated under observation.

The Urine.—Pyuria is the classical sign of pyelonephritis. The patients

[illegible]

nephritis the number may range from 30 million upwards. However, the disease may pass through stages in which the inflammatory process is quiescent or extinguished (healed stage of Weiss and Parker) and the urine is clear with few leucocytes in the sediment. This is especially apt to occur in long-standing cases in which the clinical picture is dominated by

The face may be slightly puffy, but marked edema is rare and usually has a cardiac component in its pathogenesis. The combination of proteinuria, even modest, and anorexia often results in hypoalbuminemia; the globulin content of the serum is usually increased, presumably partly as a result of the infection. In children, chronic pyelonephritis may be associated with renal osteodystrophy (page 626). With azotemia, anemia develops. The infection may result in moderate leucocytosis and the sedimentation rate may be accelerated.

Pyelographic Findings.—The intravenous pyelogram, of course, affords a valuable index of renal excretory function. The contour of the pyelogram may or may not be altered in chronic pyelonephritis. Nesbit and Conger

cent, minimal changes in 54.7

and marked changes in 7.5 per

The changes consist in various

dilatations, constrictions or distortions of the pelvis and ureters. In the hematogenous cases the pelvis is most often decreased in size. There may be diminution in the size of the renal shadows. In the cases not secondary to disease of the urinary passages, cystoscopy usually reveals little change in the bladder.

signals the last stage of the disease. However, as mentioned above, the progress of impairment of renal function is often extraordinarily slow in chronic pyelonephritis, and the patient may be active for several years with moderate azotemia. The hypertension not rarely goes into the malignant phase, in which event the course is usually rapidly downhill with death in less than two years after the retinal lesions have appeared. When pyelonephritis is secondary to some such lesion of the urinary passages as urolithiasis, prostatic enlargement or stricture of the urethra, removal of the obstruction may be followed by clearing of the renal disease. Unfortunately, this is not always the case, not rarely, pyuria persists after prostatectomy or other elimination of a causative lesion. Pyelonephritis of pregnancy most often clears up completely, but not rarely persists as the chronic disease or recurs with succeeding pregnancies.

Statistics of the outcome of pyelonephritis vary widely, probably largely because of inclusion of cases of different causation. The proportion of patients recovering completely is much higher when pyelonephritis is secondary to such lesions of the urinary tract as urolithiasis or prostatic enlargement which can be removed than in the hematogenous cases first seen in the chronic stage. Braasch and Cathcart[18] found that one th

treatment, the proportion of recoveries in chronic pyelo-

sociates has shown that chronic pyelonephritis may so impair sodium and chloride conservation by the tubules that a "salt-losing nephritis" results with a clinical picture simulating adrenocortical insufficiency.

Uremia.—As already mentioned, the initial complaints may be uremic. A considerable fraction of the patients ultimately succumbs to uremia. The progress of the renal insufficiency is usually very slow and punctuated by periods esult of treatment. Weiss and after the development of uremic pericarditis; this I have not observed. The uremic manifestations do not differ from those in other forms of renal disease.

Hypertension.—It was pointed out by Longcope, Weiss and Parker and blood pressure. Bell[15] as due to a complica- experience. It is true that hypertension does not occur in acute pyelonephritis, but it develops in a high proportion and in a majority of mendous hypertension Butler[16] found an average blood pressure of 190/140 mm. in 7 children between three and eleven years with chronic pyelonephritis. In these cases in children there can be no doubt that the hypertension results from the pyelonephritis. Braasch and Jacobson[17] found that in patients with chronic pyelonephritis under the age of fifty, hypertension is twice as frequent as in controls The hypertension may be of the utmost severity and enter the malignant phase with resultant retinopathy, encephalopathy and renal arteriolar necrosis. While necropsy may reveal hyalinization of the renal arterioles and endarteritis of the small renal arteries in chronic pyelonephritis with hypertension, this is not always the case (Longcope, Weiss and Parker, own observations). Such observations show that chronic pyelonephritis, like glomerulonephritis, may cause hypertension without the intermediacy of arterial or arteriolar lesions. Hypertension may result from unilateral pyelonephritis (see below).

Heart failure may develop in patients with chronic pyelonephritis and hypertension. While major coronary thrombosis or cerebro-vascular accidents may complicate pyelonephritic hypertension, this has been decidedly uncommon in my experience.

Local Symptoms.—Pains in the loins or flanks are very common and are sometimes accompanied by percussion tenderness. Many patients with pyelonephritis have for years attributed their backache to "lumbago," gynecologic conditions, etc. Abdominal pains are not very rare, and such patients have undergone laparotomy. Dysuria and other symptoms of cystitis are often initial manifestations and may occur at any time of the disease.

General Manifestations.—The general health may remain excellent for years despite constant pyuria. But weakness, anorexia and emaciation may appear even before there is azotemia and are usually accelerated after the latter appears, although there are surprising exceptions in which patients are able to work with few complaints despite moderate nitrogen retention. With hyposthenuria the skin usually becomes dry and inelastic.

115/75 mm. A second, similar case was included in Butler's pioneer communication. Butler's paper awakened great interest in the subject of hypertension due to unilateral kidney disease and many cases were published of variegated etiology (pyelonephritis of calculous or other etiology, hydronephrosis, narrowing or occlusion of the renal artery, renal tuberculosis, perinephritis, Wilms' tumor, etc.). Unilateral renal disease was assiduously sought for in patients with seeming essential hypertension. A great many unilateral nephrectomies were performed with the object of

tension (*cf.* Bell[16]). The subject is reviewed in detail by Smith.[20] While

the cause of the high blood pressure. Completely obscure is the reason why high blood pressure occurs in some instances of unilateral pyelonephritis and is absent in the larger moiety However, the fact that some patients with glomerulonephritis do not have high blood pressure causes no one to doubt that glomerulonephritis can elevate the bl[illegible]

[illegible] originally the result of the unilateral renal lesion. There are observations in rabbits with hypertension due to constriction of one renal [illegible]

[illegible] the interesting study of Weiss and Chasis[21] on a patient with hypertension and unilateral renal disease Following nephrectomy, which failed to affect the blood pressure, they found that the remaining kidney showed *supernormal* blood flow, glomerular filtration and tubular secretion

Unilateral nephrectomy for the treatment of hypertensive disease was greatly overdone in the first years after Butler's paper. It should be carried out only after the most careful consideration There should be no evidence of disease of the other kidney, the function of which should be faultless And the function of the affected kidney should be absent or insignificant. For the proportion of even meticulously selected cases in which unilateral nephrectomy abolishes hypertension is small, and with persistent hypertension one is in no position to sacrifice even a small

nephritis is much higher. Such recoveries, however, occur almost solely among the cases treated before the onset of significant impairment of renal function or hypertension. When these manifestations are present, while pyuria and bacteriuria may be suppressed, though they often recur, the renal damage progresses and most of the patients ultimately succumb to uremia or less often the consequences of hypertension. However, the course is often protracted for many years. Raaschou found that about one-third of patients with pyelonephritis succumb to uremia and about one-sixth to consequences of arterial hypertension. Chronic pyelonephritis usually lasts so many years that many of the cases fall victim to unrelated disorders.

Treatment.—Several lines of treatment come into consideration in chronic pyelonephritis:

1. Every patient should receive careful urological study. If the renal lesion is secondary to urolithiasis, prostatic enlargement, infection of the lower genital or urinary tracts, congenital anomalies, etc., these should receive appropriate treatment. An acute exacerbation during pregnancy may call for ureteral catheterization.

2. The urine should
smear. If an organism
ment with antibiotics,
urine should be instituted. The nature of the antibacterial treatment is guided by tests of the sensitivity of the organism to the different agents.

The antibacterial treatment should be intensive and protracted in the effort completely to eliminate and not merely to suppress the infection. Unfortunately, this goal often can not be attained. Especially in the use of sulfonamides, it should be borne in mind that when renal function is

Even if a pathogenic organism can not be demonstrated in the urine, antibacterial treatment should be administered if fever or pyuria indicate that infection is still present.

3. Impairment of renal function and uremia are to be managed as in other diseases (page 223). The same is true of heart failure, anemia and other manifestations.

4. The question of nephrectomy in unilateral pyelonephritis is discussed in the next section.

Hypertension Due to Unilateral Pyelonephritis.—Cases in which high blood pressure results from unilateral chronic pyelonephritis or other unilateral renal

His patient was a boy of seven years with a stone in the right ureter, which was removed. At the time, the blood pressure was 98/50 mm. Right hydronephrosis was present and right pyelonephritis developed. The blood pressure rose as high as 168 mm. systolic and 110 mm. diastolic. Right nephrectomy was followed by return of the blood pressure to normal, in the twenty months after operation the blood pressure was never over

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amount of functioning kidney. Needless to say, the physician should take pains to make clear that the chances of helping hypertensive disease by unilateral nephrectomy are not great. But if one kidney is nonfunctioning and the other faultless, the risk of the operation is small, removal of the kidney constitutes no loss, and even a rather small possibility of help may be worthwhile. If nephrectomy is indicated on urological grounds, the presence of hypertension is not a contraindication.

In several series in the literature (*cf.* Smith), the incidence of hypertension is not significantly greater in urologic disease than in controls. This, however, does not prove that urologic disease never participates in the pathogenesis of hypertension. The nature of renal hypertension is not elucidated (Chapter 10) and it may be that urologic disease may set in action mechanisms which counter as well as favor elevation in blood pressure. When urologic disease in young children is accompanied by such blood pressures as 220/150 mm., there would seem to be no reasonable doubt of the connection.

Necrotizing Pyelonephritis in Diabetes Mellitus.—Infection of the urinary tract and pyelonephritis are more common in diabetics than in others. Baldwin and Root[22] found that about 20 per cent of patients succumbing to diabetes have infections of the
now that antibiotics are availab
culture bacteria from the urine of
from controls. Urinary infection in the diabetic may be manifested merely by asymptomatic pyuria lasting months or years and often responding readily to antibacterial treatment, though with marked tendency to recur. In unusual cases, however, severe pyelonephritis develops, which may run a fulminant and rapidly fatal course due to either renal insufficiency with uremia or overwhelming infection. There may be septic fever, chills and bacteriemia. Anatomical examination in fatal cases reveals suppurative and necrotizing pyelonephritis with thromboses in the small vessels. The necrosis is especially apt to involve the renal papillæ. However, necrosis of the renal papillæ is not a specifically diabetic lesion, Robbins[24] *et al* found that of 26 cases with necrotizing papillitis, 7 were in nondiabetics. Experimentally, renal papillary necrosis has been produced in the rabbit by the combination of ureteral ligation and intravenous injection of bacteria (Mallory[25] *et al*) and in the dog by ureteral ligation alone (Muirhead *et al.*[26]).

According to Harrison and Bailey, necrosis of the renal papillæ is manifested in the pyelogram by an irregular filling defect which strikingly resembles that in renal tuberculosis. In several cases the diagnosis of renal papillary necrosis has been made by examination of bits of tissue voided in the urine (Johnston[27])

Fulminating pyelonephritis in diabetes seems to have become much rarer since the introduction of antibiotics. The cases probably can be largely prevented by antibacterial treatment of low grade urinary infections.

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it is to be emphasized that *independent* glomerular, tubular, ... lesions are all usually present in such cases, though any one may pre- ... the term *focal nephritis*

ferentiation is difficult in some cases and impossible in others ... the fact remains that in patients with almost any infection hematuria, proteinuria and cylindruria may occur and necropsy reveal *only* the focal lesions described in this chapter with none of the diffuse changes of glomerulonephritis. Clinically, the differentiation is important. For example, when red blood cells are found in the urine in such conditions as viral pneumonia or typhoid fever, the clinician knows that the urinary findings bespeak what is here termed focal nephritis, which will hardly influence the course of the primary disease, and the chances are exceedingly small that they herald the onset of glomerulonephritis with its uncertain outlook. Theoretically, also, the distinction between focal nephritis and diffuse glomerulonephritis is important. It was seen in Chapter 10 that glomerulonephritis is *not* due to the invasion of the kidneys by microorganisms, but that allergic factors are concerned in its causation. On the other hand,

nephritis

to chemical poisoning, focal nephritis is a manifestation of infection. Moreover, it *occurs at the height of the infection*. Herein lies, as Volhard[8] pointed out, an important difference between focal nephritis and acute glomerulonephritis, for the latter most often, though not invariably, occurs after the primary infection has started to subside, as is seen in glomerulonephritis complicating scarlet fever and often tonsillitis. The close linkage of focal nephritis to the height of the infection is well illustrated by the old observation of Kannenberg[9] that in focal nephritis complicating relapsing fever, the renal process waxes and wanes with the periods of the disease.

be due to the direct action of microorganisms on the renal structures. The correctness of this view is substantiated by two other lines of evidence.

Chapter

23

FOCAL NEPHRITIS, ACUTE INTERSTITIAL NEPHRITIS, AND FOCAL GLOMERULAR LESIONS IN SUBACUTE BACTERIAL ENDOCARDITIS*

FOCAL NEPHRITIS

DURING the course of various infections, there may appear in the urine—which was previously normal or presented only the characteristics of febrile proteinuria—blood, larger amounts of protein, and numerous casts. Edema and hypertension are absent, and impairment of renal function is very rarely significant. Indeed, there is almost always little or no evidence of a renal lesion apart from the urinary findings, and the course of the primary disease is generally not notably influenced. Anatomically, there are *focal* inflammatory and regressive lesions in the glomeruli, tubules, and interstitium.

In the past, such cases have generally not been clearly differentiated from acute glomerulonephritis—both being grouped with the focal glomerular lesions of subacute bacterial endocarditis under the collective term of acute hemorrhagic nephritis—though they differ distinctly from the latter pathogenetically, anatomically and, as a rule, clinically. Focal nonembolic nephritis was first adequately differentiated by Scheidemandel[1] and Volhard and Fahr.[2] The latter expressed their conception of the nature of the process in the term *focal glomerulonephritis*. During World War I, Munk[3] made an exhaustive study of the occurrence of this variety of renal disease, and spoke of it as "Infektnephritis." In this country, Baehr[4] published a study of 14 cases of the disease here under consideration. Christian[5] and his coworkers, O'Hare and Walker,[6] devoted attention to the hemorrhagic nephritides, but it does not seem to me that they differentiated sharply between glomerulonephritis and the renal lesions that form the subject of this section.

The term focal glomerulonephritis has been generally applied to this type of renal disease, but is open to the objection that the lesions differ

* The renal lesions discussed in this chapter—focal nephritis, acute interstitial nephritis, and the focal glomerular lesions of subacute bacterial endocarditis—all occur as a result of and in the presence of active bacterial infection. For this reason, their incidence has decreased enormously since the introduction of antibiotics and many of the manifestations described are of little more than historical interest where antibiotics are in general use.

removed.

Pneumonia.—Renal function is unimpaired in the vast majority of patients with pn ... and Reiman[12]). Correspondingly, it was mentioned ... monia Most o... consequence as far as the outlook for the patient is concerned, though ... tend to occur in very severe cases. The hematuria diminishes rapidly with the drop in temperature or before. The rare instances of glomerulonephritis complicating pneumonia were mentioned above (page 534)

Typhoid Fever —Febrile proteinuria was present in 66 per cent and casts in 37 8 per cent of Osler's 1500 cases, they are of little significance Curschmann[13] found acute nephritis in 1 per cent and Jochmann[15] in 3.5 per cent of their cases of typhoid fever It is probable that almost all these cases were instances of focal nephritis, in fact, so experienced a pathologist as Fahr[16] states that he has never seen glomerulonephritis attributable to typhoid bacilli In the extremely rare instances, as those described by Howland,[17] in which glomerulonephritis does complicate typhoid fever, it is probably either a reactivation of chronic glomerulonephritis, which occurred in a case observed by Munk, or the result of secondary infection

Anatomically, focal nephritis is found These cases were long ago studied by Wagner,[18] who differentiated two groups In the first, focal, ...te, while in the second inter... feature The interstitial in... formation of miliary abscesses, ... cases of typhoid fever. Munk also describes a third group in which there is extensive necrosis of the tubular epithelium Typhoid bacilli may be found in the lesions and in the lumen of the tubules

Other Infections —Focal nephritis occurs on very rare occasions in various other infectious diseases—scarlet fever, measles, cerebrospinal ... sitory

..., focal nephritis occurs with much greater frequency in malaria and relapsing fever, with the first of these diseases the writer has had little personal experience and with the second none

Malaria —Thayer[19] found 26 instances of acute nephritis in 1032 cases of malarial fever Seven of these occurred in tertian fever, 1 in quartan, 6 ...er hand ...at renal ...4 23 per ...ose with quartan fever Contrary to these investigators, Munk[21] did not observe

1. At necropsy, the causative organism (streptococcus, pneumococcus, typhoid bacillus, malaria plasmodium, etc.) can frequently be demonstrated in the renal lesions. This has recently been denied by Allen,[10] but many years ago, when these lesions were carefully studied at Mount Sinai Hospital, organisms were repeatedly demonstrated in focal nephritis complicating streptococcic and other infections.

2. Cultures of the urine taken with appropriate precautions often reveal the presence of the causative organism, which is also in contrast to the vast majority of cases of acute glomerulonephritis. Thus, streptococci have been found many times in the urine of patients with focal nephritis complicating tonsillitis (Scheidemandel[1] and others), and may even be so numerous as to be seen readily in the stained sediment. The presence of typhoid bacilli in the urine in focal nephritis complicating typhoid fever is, of course, not of great significance.

The evidence is thus very strong that focal nephritis results from the presence in the kidneys of microorganisms which have been brought there by the blood stream from a distant focus. In fact, in a case in Mount Sinai Hospital of focal nephritis complicating tonsillitis, streptococci were cultivated from the blood. Focal nephritis is, then, more closely related to the focal glomerular lesions of subacute bacterial endocarditis and to multiple hematogenous abscesses of the kidneys than to glomerulonephritis, which is of toxic origin. On histological examination of kidneys containing hematogenous abscesses, it is not uncommon to find widely distributed focal nephritis.

It has been suggested that the lesions of focal nephritis are caused by bacteria in the process of excretion into the urine (Ausscheidungsnephritis of the Germans). Such a conception would account for the fact that when focal nephritis complicates, for example, tonsillitis, there is no clinical evidence that the bacteria disseminated from the tonsils by the blood stream have produced lesions in organs other than the kidney. But it is to be remembered in this connection that discrete inflammatory and necrotic foci akin to those in the kidneys are common in different organs (*e. g.*, the bone-marrow and the liver) in the course of various bacteremias, and generally give no clinical evidence of their presence. In the kidney, however, the examination of the urine reveals the lesions. So it may be, and in some instances this is undoubtedly true, that focal nephritis is but one manifestation of a widespread process.

The incidence of focal nephritis in various infections is considered in the following:

Streptococcal Infections – Tonsillitis and other varieties of angina were formerly a common cause of focal nephritis, though since the introduction of antibiotics the complication is rarely seen. The hematuria appears at the height of the process in the throat and generally quickly subsides. But it is in the cases that complicate sore throat that the obstinate persistence of microscopic hematuria over long periods of time is most often encountered. The reason, quite probably, is that the infectious focus in the throat, though giving no marked local symptoms, continues to send bacteria into the blood stream.

Erysipelas is rather rarely complicated by acute nephritis—8 times in [illegible] 163 cases. The large majority of nephritides complicating [illegible] accompanied by focal nephritis, which generally quickly clears up if the primary focus is removed

PNEUMONIA —Renal function is unimpaired in the vast majority of patients with pneumonia (MacIntosh and Reiman[12]). Correspondingly, it was mentioned above that all varieties of acute nephritis are rare in pneumonia Most of the few cases observed are focal nephritides and of little consequence as far as the outlook for the patient is concerned, though they tend to occur in very severe cases. The hematuria diminishes rapidly with the drop in temperature or before The rare instances of glomerulonephritis complicating pneumonia were mentioned above (page 534).

TYPHOID FEVER —Febrile proteinuria was present in 66 per cent and casts in 37 8 per cent of Osler's 1500 cases, they are of little significance Curschmann[14] found acute nephritis in 1 per cent and Jochmann[15] in 3.5 per cent of their cases of typhoid fever It is probable that almost all these cases were instances of focal nephritis, in fact, so experienced a pathologist as Fahr[16] states that he has never seen glomerulonephritis attributable to typhoid bacilli In the extremely rare instances, as those described by Howland,[17] in which glomerulonephritis does complicate typhoid fever, it is probably either a reactivation of chronic glomerulonephritis, which occurred in a case observed by Munk, or the result of secondary infection

Anatomically, focal nephritis is found. These cases were long ago studied by Wagner,[18] who differentiated two groups In the first, focal, hemorrhagic glomerular lesions predominate, while in the second interstitial infiltration is the most prominent feature The interstitial infiltration may go on to softening and the formation of miliary abscesses, these were present in 7 of Osler's 137 fatal cases of typhoid fever Munk also describes a third group in which there is extensive necrosis of the tubular epithelium Typhoid bacilli may be found in the lesions and in the lumen of the tubules

OTHER INFECTIONS —Focal nephritis occurs on very rare occasions in various other infectious diseases—scarlet fever, measles, cerebrospinal fever, influenza, rheumatic fever, and many others In all, it is transitory and of little significance

It should be mentioned, however, that according to the literature, focal nephritis occurs with much greater frequency in malaria and relapsing fever, with the first of these diseases the writer has had little personal experience and with the second none

Malaria —Thayer[19] found 26 instances of acute nephritis in 1032 cases of malarial fever Seven of these occurred in tertian fever, 1 in quartan, 6 in æstivo-autumnal, and 1 in an uncertain type On the other hand Giglioli,[20] in his extensive studies in British Guiana, found that renal disease did not complicate æstivo-autumnal fever but occurred in 4.23 per cent of his patients with tertian malaria and 48 57 per cent of those with quartan fever Contrary to these investigators, Munk[21] did not observe

any instance of renal disease in several thousand cases of malaria studied in Europe during World War I. Evidently, there are variations in the incidence of renal disease in different groups of cases of malarial fever; the nature of the treatment may also play a part. It should be borne in mind [illegible] malaria.

Anatomical studies have been made by Kiener and Kelsch,[23] Barker,[24] Ewing,[25] and by Italian observers. While in some of the cases, true glomerulonephritis is present, in most the description seems to be that of focal nephritis, which is often very widespread. In an interesting case studied by Ewing, there were extreme degenerative changes and extensive hemorrhages which resulted from the enormous accumulation of parasites in the renal capillaries. Pigmentation of the glomeruli is often found whether or not nephritis is present. Some of the cases become chronic, and Thayer is of the opinion that in lands infested with malaria, it may play a not unessential part in the etiology of chronic renal disease. It would seem that a study of the pathological anatomy of these chronic malarial nephritides in regions where such material can be obtained would probably be of great interest, for it might yield information as to what changes are produced by a chronic, recurrent, focal nephritis, a condition about which nothing is known.

Clinically, the cases of focal nephritis exhibit little more than the presence of blood, protein, and casts in the urine. It seems that exceptionally the focal lesions are sufficiently widespread to produce uremia. However, the symptoms of focal nephritis and glomerulonephritis are not differentiated in the older literature.

Relapsing Fever.—Kannenberg[9] found acute nephritis in 8 of 39 cases of relapsing fever. Ponfick[26] and Puschkareff[27] observed renal lesions almost constantly in patients who died in epidemics of relapsing fever. While some of the cases may have been glomerulonephritis, as indicated by the presence of edema, the majority seem to have been focal nephritis. In an investigation in Poland, during World War I, Munk[28] found the renal lesions in relapsing fever to be focal nephritis.

Chemical Posioning.—Chemical poisoning not uncommonly produces focal nephritis. Arsenic, cantharides and various other nephrotoxic substances may cause focal lesions in the kidney, clinically manifested chiefly by hematuria, and clearing up rapidly after the noxious substance has been withdrawn.

Pathological Anatomy.—There is nothing characteristic in the gross appearance of the kidney in focal nephritis; the type of lesion present is, as a rule, first ascertained with the microscope. The kidney may be normal in size or somewhat enlarged, rather soft, and the capsule strips readily. The surface generally appears rather congested and in very severe cases is chocolate colored. The most striking feature is usually the presence of small hemorrhages, which may be few in number or very numerous. The surface of the section is moist, the architecture little altered, and the glomeruli stand out as dark or bright red points.

Microscopically, it is seen that most of the glomeruli are normal, apart
some, however, there are lesions. The most

... free from such change. ...

may be seen, particularly over an area of nuclear ...
tuft. In some of the capsular spaces which do not contain blood, there



Fig 36 —Focal nephritis Hemorrhage into capsular spaces and tubules and foci of tubular destruction with cellular infiltration

may be coagulated exudate But it is to be emphasized that many, and in fact most often considerably the greater part, of the glomeruli are unaltered

The epithelium of the tubules in most cases shows cloudy swelling In severe processes, there may be focal necroses of the tubular epithelium, in which the nuclei do not take the stain Necrosis was very extensive in some exceedingly severe cases of typhoid fever studied by Munk. There are usually foci of fatty change and desquamation of the tubular epithelium, but these are not extensive. Some of the tubules contain blood, and others granular débris or well-formed casts, but the latter are generally not

As a rule, scattered interstitial infiltrates, largely of lymphocytes, are present; they may be around the glomeruli. Small interstitial hemorrhages are present in many instances. The vessels are unaltered apart from the usually well-marked congestion of the intertubular capillaries.

Bacteria (streptococci, pneumococci, typhoid bacilli, etc.) can often be demonstrated in the lesions and sometimes in the lumen of the tubules.

Symptomatology.—In the vast majority of instances focal nephritis is merely an incident in the course of an infectious disease, not influencing the course of the primary malady, and discovered only as a result of the urinary abnormalities.

Hematuria is the cardinal symptom. It usually appears at the height of the infectious process (tonsillitis, erysipelas, scarlet fever, typhoid fever, etc.). Most of the cases exhibit only microscopic hematuria; since the introduction of antibiotics, hematuria visible to the naked eye has become very rare. The duration of the hematuria is variable; it generally diminishes after a few days, but isolated red cells may be found in the sediment for long periods. Improvement in the primary disease is most often quickly followed by diminution in the hematuria, if it has not previously cleared up. When the fever is quickly terminated by an antibiotic, the red cel

generally but moderate in quantity, and varying numbers of hyaline, granular and blood casts. Leucocytes are often abundant and there may be epithelial cells It is not uncommon to find bacteria in the stained sediment, particularly in cases complicating tonsillitis.

Renal function is unimpaired in the vast majority of instances. However, Volhard mentions a case with transitory impairment of renal function, in such instances, the foci must be extremely numerous. As a rule, the urinary volume is diminished, presumably as a result of the fever

The absence of edema and hypertension is a basic criterion for the diagnosis. Hypertensive retinopathy is, of course, likewise absent

Occasionally, there is pain in the lumbar region, as a rule transitory and not severe.

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fever. Almost always, it causes no symptoms apart from the urinary abnormalities and does not in itself influence the outlook. The onset of the hematuria is most often during the fastigium, and it clears up rapidly with defervescence. There is neither hypertension nor edema, and it may be questioned whether the so-called uremia which is described in the older works was actually such or a manifestation of typhoid toxemia The mortality is relatively high in typhoid fever complicated by focal nephritis apparently because this complication occurs mostly in previously severe cases. Jochmann[15] observed 50 per cent mortality in such patients, but other clinicians have not noted so high a rate.

There are extremely rare instances in which the manifestations of severe focal nephritis mark the onset of typhoid fever, the *Nephrotyphus* or *fièvre typhoide à forme renale* of Continental authors. I have seen one such

ase, in which the patient was admitted to Mount Sinai Hospital with the diagnosis of acute nephritis because of the marked hematuria and was revealed only after several days to be suffering from typhoid fever. The patient recovered, though the prognosis in "Nephrotyphus" is generally stated to be very bad

Diagnosis.—The diagnosis of focal nephritis rests on the appearance during the course of an acute infectious disease of hematuria, proteinuria and cylindruria in the *absence of edema and hypertension.* Impairment of renal function is extremely rare in focal nephritis. Of course, there are

nephritis was present. It should be remembered that glomerulonephritis is extremely rare as a complication of other than streptococcal infections. The differentiation between acute glomerulonephritis and focal nephritis

in severe cases.

In unusual instances of focal nephritis complicating tonsillitis, slight hematuria, usually only microscopic, may persist for long periods, even

Treatment.—The treatment is that of the primary infection, the renal condition requiring no special therapeutic measures. In the cases complicating tonsillitis, it is well not to remove the tonsils during the acute stage of the renal process, for the operation is often followed by increase in hematuria and, according to Scheidemandel,[1] of the number of bacteria in the urine After the blood has disappeared from the urine, diseased tonsils should be removed If slight hematuria is very persistent, tonsillectomy should be carried out, though it is possible that the amount of blood in the urine will increase for several days, but this soon disappears. Baehr[4] observed a case of focal nephritis which was cured by repeated washings of the infected antrum of Highmore.

ACUTE INTERSTITIAL NEPHRITIS

We have seen that there is no adequate justification for the use of the term chronic interstitial nephritis as commonly applied to those renal diseases which are characterized clinically by arterial hypertension and its consequences in the absence of edema and anatomically by extensive fibrosis of the kidneys There is, however, an acute interstitial nephritis, though it can rarely, if ever, be recognized *intra vitam.* Councilman[29] defines the condition as follows "An acute inflammation of the kidney characterized by cellular and fluid exudation in the interstitial tissue,

accompanied by, but not dependent on, degeneration of the epithelium; the exudation is not purulent in character, and the lesions may be both diffuse and focal." According to Councilman, the first case of acute interstitial nephritis was published by Biermer[30] in 1860, though Biermer's description does not seem unequivocal to me. The renal lesion was later described by Wagner[18] under the name of acute lymphomatous nephritis; however, under this term he also included some cases of the variety here known as focal nephritis. The best anatomical study is that of Councilman.

As would be anticipated from the importance of septic infection in its etiology, acute interstitial nephritis has diminished greatly in frequency since the introduction of antibiotics. I have not seen a case in several years.

Etiology.—Acute interstitial nephritis complicates septic states, notably secondary streptococcal invasions in the acute specific infectious diseases of childhood. Thus, Councilman found acute interstitial nephritis at necropsy in 24 of 100 cases of diphtheria, 5 of 20 of scarlet fever, 5 of 23

complicated by secondary infections with bacteremia, and that the incidence of acute interstitial nephritis in non-fatal cases is undoubtedly far smaller. Acute interstitial nephritis also occurs in rare cases of sepsis following sore throat, erysipelas, typhoid fever, smallpox, infected wounds, etc. In addition to its occurrence in septic states, Kimmelstiel[32] observed extensive interstitial cellular infiltration in hemolytic reactions, especially following blood transfusion, and in the hepato-renal syndrome. As mentioned above, the frequency of acute interstitial nephritis has diminished greatly since the introduction of antibiotics. However, Allen[33] found that acute interstitial nephritis may be a manifestation of sulfonamide reactions.

mortem invasion. Not uncommonly streptococci can be demonstrated in sections of the lesions

Duval and Hibbard[34] have produced acute interstitial nephritis in the dog by inoculation with living cultures of scarlet fever streptococci. This finding contrasts with the glomerular lesions which they produced by the toxic filtrate in the absence of the living organisms (page 557) and indicates that acute interstitial nephritis is due to invasion of the kidneys by the organisms rather than to the action of the toxic products as in glomerulonephritis On the other hand, Kimmelstiel, who observed acute interstitial nephritis in association with hemolytic reactions and acute liver damage, regards it as a hyperergic response to protein products. Allen's observations of acute interstitial nephritis in sulfonamide reactions have similarly led him to regard it as of allergic pathogenesis That other organs than the kidney are also sometimes involved will be pointed out below.

Pathological Anatomy.—In most instances the macroscopic appearance of the kidney is not characteristic. It is enlarged, often very considerably,

and soft
various siz
ing of the
normal ma...
hemorrhages in the cortex between which are yellowish areas, thus producing a striated appearance which Aschoff[16] considers as very characteristic.

Microscopically, one is immediately struck by the presence of dense cellular infiltration. The cells lie closely packed between the tubules and around the glomeruli. The distribution of the infiltrates is irregular; in some places they seem diffuse, while elsewhere the focal arrangement is very obvious. In other cases, there may be only isolated nodular infiltrates.

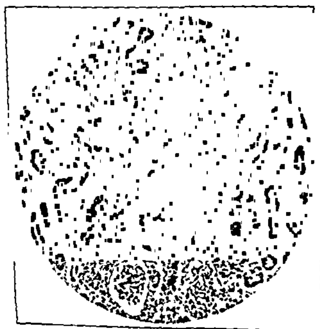


FIG 37.—Acute interstitial nephritis in a child, aged eighteen months, with sepsis. Extensive infiltration of plasma cells and lymphocytes in the interstitium.

According to Councilman, the lesions are most marked in the boundary zone of the pyramids, next under the capsule, and thirdly, around the glomeruli. In many areas, the exquisitely interstitial nature of the infiltration is seen, the masses of cells separate the individual ...
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... and other changes in the glomeruli are to be

seen. There are also hemorrhages, often of linear distribution at the borders of the infiltrates. Groups of tubules may contain blood.

The nature of the cells composing the infiltrates varies in different cases. Councilman points out that in many instances the infiltrating elements are almost all plasma cells. Very commonly, however, lymphocytes predominate. There are few polymorphonuclear leucocytes in the lesions. But according to Huebschmann,[36] polymorphonuclears may predominate in the first stage. Munk[37] observed a case of acute interstitial nephritis complicating hemorrhagic smallpox in which there were numerous eosinophiles in the infiltrates.

The rare cases of *acute interstitial edema* of the kidneys are probably closely related to acute interstitial nephritis. In a case of this type that I saw some years ago, the clinical picture was that of a febrile infection with fulminant renal insufficiency.

Pathogenesis.—Councilman and Schridde[38] have shown that the cells composing the infiltrates emigrate from the blood vessels, *i.e.*, that the inflammation is predominantly exudative rather than proliferative. That the exudative process is not confined to the kidneys is indicated by the investigations of Landsteiner,[39] who has shown in cases of acute interstitial nephritis complicating scarlet fever that histologically similar infiltrates are to be found in the suprarenals, liver meninges, and other organs. The above-mentioned case described by Munk of acute interstitial nephritis complicating smallpox, in which one-third of the infiltrating cells were eosinophiles, is very

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to those in the kidney in other organs, Munk looks upon acute interstitial nephritis not as a pure kidney disease but as a generalized cellular exudation caused by the

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plasma cells,

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organs, thereby indicating the unity of the process. Further investigations

in various organs, but in other cases no extrarenal infiltrates were found.

Clinical Picture.—Acute interstitial nephritis is first recognized with certainty at the postmortem table, for the disease produces no characteristic manifestations during life. It occurs most often in the course of severe septic infections, and even in retrospect it is often impossible to discern any notable influence of the renal lesion on the clinical course. There is neither hypertension nor edema. Even proteinuria may be slight or absent. Occasionally, there is hematuria. The urinary volume is usually diminished, but often not beyond the degree that might be expected in any highly febrile patient. Rarely, there is complete anuria, as in Biermer's original patient, who passed practically no urine for ten days. In such unusual cases enormous nitrogen retention may occur (Noble[40]) and death is due to uremia.

Because of our inability to recognize acute interstitial nephritis during e, it is not known how many patients recover. It would seem that sur- ... for so far as is known, acute interstitial nephritis ... which ... of case

pathogenesis of contracted kidney manifesting itself many years later Aschoff[40] believes that some instances of contracted kidney may be traced with "probability" to antecedent acute interstitial nephritis. I know of no evidence that this actually occurs. Loewenthal[41] described a case of what he considered as true chronic interstitial nephritis, but considered that it was alone in the literature Rich[42] published 19 cases of interstitial ...

ating *between* the nephrons, appa

Diagnosis.—As stated above, ... nephritis is almost impossible during the ... sets in during the first week of septic scarlet fever, before the period when glomerulonephritis occurs, the existence of acute interstitial nephritis may be suspected

Prognosis and Treatment.—Since the diagnosis cannot be made with any assurance, the prognosis and treatment are of necessity those of the primary disease If the renal condition could be recognized or very strongly suspected, and the oliguria was extreme, decapsulation would seem logical in view of the swelling of the kidney But since the antibiotics came into use, acute interstitial nephritis seems to have practically disappeared

FOCAL GLOMERULAR LESIONS IN SUBACUTE BACTERIAL ENDOCARDITIS

Harbitz[43] long ago noted that "hemorrhagic nephritis" is common in protracted cases of bacterial endocarditis, of the type now known as subacute bacterial endocarditis (Libman[44]) That the hematuria in these cases is usually not due to diffuse glomerulonephritis, but to focal glomerular lesions produced by minute bacterial emboli from the endocardial vegetations, was maintained by Loehlein,[45] and strongly supported by extensive material by Baehr[46] The process has been generally known as embolic non-suppurative focal nephritis (Loehlein) ...

... the grossly ... riptive term ... ised. ... e become

Etiology.—The focal glomerular lesions to be described below occur almost exclusively in subacute bacterial endocarditis. By careful searching, the lesions are found in a very high proportion of cases; Baehr observed them in 23 of 25 kidneys in subacute bacterial endocarditis due to the Streptococcus viridans. Miller and Branch[47] have also found them in a case due to an influenza-like bacillus. Focal glomerular lesions were present in a case, at Mount Sinai Hospital, of subacute bacterial endocarditis due to the pneumococcus Type II, and probably in another due to the influenza bacillus; in both these cases there was also diffuse glomerulonephritis. Focal glomerular lesions occur not only in the active phases of subacute bacterial endocarditis but also in Libman's healed stage; Baehr found the lesions in 6 of 7 healed cases.

On rare occasions, the characteristic focal lesions in the glomeruli are encountered in conditions other than subacute bacterial endocarditis. Baehr mentions one instance in which the seemingly typical lesions were present in an obscure infection without endocarditis. Bell[48] has also seen the characteristic foci in a case of sepsis from an infected wound and erysipelas but without endocarditis. And Fahr[49] describes a case of otogenous sinus thrombosis in which the histological picture of focal glomerular lesions was produced by proliferation of cocci within the glomerular loops so as to block them and result in foci of coagulation necrosis. But it is to be emphasized that such examples of morphologically typical focal lesions in the absence of endocarditis are of extreme rarity.

On the basis of the work of Loehlein, Baehr and Libman, focal glomerular lesions have been considered almost pathognomonic of subacute bacterial endocarditis. However, Bell has reported that in 3 of 104 cases of rheumatic endocarditis "capillary thromboses were found which

subacute bacterial endocarditis seems improbable, for if such were the case one would also expect to encounter the fully developed lesions in a disease of such varying duration and with so many recurrences as is rheumatic fever. According to material studied at Mount Sinai Hospital, New York, by Libman, Baehr and Klemperer, the typical embolic lesions are not encountered in uncomplicated rheumatic fever. Bell also reports finding focal glomerular lesions in 4 of 56 cases of acute endocarditis (defined as being of less than six weeks' duration) and in 4 of 69 cases of secondary endocarditis (*i. e.*, endocarditis in which a primary infectious focus is demonstrable, not recognized clinically, and presumably a terminal infection). It seems probable that at least some of these cases of "acute" endocarditis would fall within Libman's conception of subacute bacterial endocarditis, in which the *clinical*
weeks, if it is terminated by som
shortly after the first symptoms.
acterized more by the nature of the endocardial lesions than by the duration of the disease.

Pathological Anatomy.—The kidneys are normal in size or more often somewhat enlarged. The capsule usually strips readily from the smooth surface. However, in older cases there may be some irregularity of the

surface with adhesions of the capsule due to small indurated scars. The most characteristic feature, though not invariably found, is the presence of small, usually irregular hemorrhages, often very numerous, and imparting to the kidney an appearance aptly described by the term "flea-bitten" kidney, used by Horder.[50] Large and small infarcts are common, resulting from the occlusion of large vessels by emboli from the endocardial vegetations

Microscopically, the characteristic glomerular lesions are found, the same kidney generally exhibiting various stages of their development.



FIG 38 —"Flea-bitten" kidney of focal glomerular lesions in subacute bacterial endocarditis The surface is sprinkled with punctate hemorrhages.

[illegible] from 2 [illegible] n which [illegible] glomeruli varies in different parts of the [illegible] propor- Also, the lesions usually involve but [illegible]

[illegible] in any part of the tuft. This progresses

until there is a homogeneous mass which stains deeply with eosin in the ordinary hematoxylin-eosin preparation, and contains nuclei in various stages of disintegration. The lesion is thus a typical coagulation necrosis Very striking is the paucity of the cellular reaction around the lesion, though there may be a few leucocytes or slight proliferation of fixed cells adjacent to the necrotic area. But if the involved capillaries are in contact with Bowman's capsule, there is usually localized proliferation and desquamation of the epithelial cells of the visceral layer of the capsule directly over the lesion. Well defined epithelial crescents may form. Localized capsular adhesions form over the involved area. Very commonly, the injured capillaries rupture into the capsular space and fill it with blood.

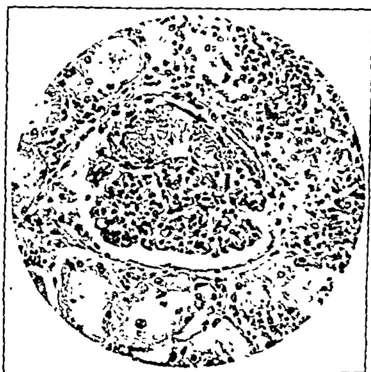


Fig. 39.—Focal glomerular lesion in subacute bacterial endocarditis Large lesion in a glomerulus Note the normal appearance of the rest of the glomerulus and the absence of inflammatory reaction about the area of necrosis.

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be the only ones present Healing of the lesions is marked by connective-tissue replacement of the necrotic area. The resultant scar, which ultimately becomes hyaline, is sharply demarcated from the rest of the glomerulus and merges with the interstitial connective tissue outside of the capsule. Loehlein points out that when an entire glomerulus is thus obliterated, the resulting hyaline area often differs from that in diffuse glomerulonephritis in that the transition to the surrounding tissue is gradual and not sharply defined.

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some instances only one or the other was found.

As a rule, some of the tubules contain blood. Baehr has found in serial sections that these tubules lead to injured glomeruli In cases with few glomerular lesions, the tubules likewise show little change. But when the glomerular lesions are widespread, there may be fairly extensive areas
n show well-marked fatty change.
Ultimately, in cases of sufficiently
lisappear completely and areas of
There is often considerable lympho-
cytic and leucocytic infiltration of the newly-formed connective tissue The atrophic changes in the tubules, which are always patchy and usually not prominent, are evidently secondary to the destruction of the appertaining glomerulus That the atrophy is ever prominent enough to lead to a notable degree of contraction of the kidney, has not, so far as I am aware, been demonstrated.

On the basis of anatomical observations by Lochlein and Baehr, it was

... able to produce glomerul...
subacute bacterial endocarditis by the intracardiac injection of an agar suspension of the Streptococcus viridans Kinsella and Sherburn[52] also noted glomerular lesions in conjunction with experimental streptococcus endocarditis

Contrariwise, many have doubted the embolic nature of the lesions (Longcope,[53] Jungmann,[54] Allen[55]) Evaluated against the embolic pathogenesis have been the great difficulty of demonstrating bacteria in the lesions and their absence in acute bacterial endocarditis. Longcope considered the possibility that the lesions represent focal allergic reactions. But to the writer the fact that the lesions occur almost exclusively in

necrosis of the capillary wall with resultant thrombosis.

Clinical Findings.—In the vast majority of cases the only clinical manifestation of the focal glomerular lesions is hematuria. Either the patient or the doctor may notice that the urine is bloody, or far more often the red cells are first revealed by microscopic examination of the sediment. The hematuria varies greatly in most instances, diminishing or even disappearing one day to return again. In other cases, it is persistent for months The quantity of blood thus lost is generally not great; sudden, copious hematuria points to gross infarction, being then often accompanied by the characteristic pain. In addition to blood, the urine contains casts of various sorts and protein, usually moderate in amount.

The course of subacute bacterial endocarditis is hardly ever modified by the focal glomerular lesions. There is neither hypertension nor edema as a result of this variety of renal lesion. Baehr found also that it does not produce impairment of renal function. An exception is constituted by rare cases in which the focal glomerular lesions are so widespread that renal insufficiency results, as manifested by diminution in concentrating power and retention of urinary constituents in the blood. Such cases have been described by Bell, Boyarsky[56] *et al.*, and others. How rarely focal glomerular lesions produce renal insufficiency may be appreciated from the fact that in over 800 cases of subacute bacterial endocarditis, Dr. Emanuel Libman told me that he had never observed it. Since antibiotics came into use, renal insufficiency is not as rare a complication of subacute bacterial endocarditis (*cf.* Villarreal and Sokoloff[58]), but, while focal lesions may be present, glomerulonephritis is then almost always present

Diagnosis.—The occurrence of persistent hematuria, microscopic or macroscopic, in a patient with subacute bacterial endocarditis immediately suggests the presence of focal glomerular lesions; in fact, on very rare occasions, the existence of subacute bacterial endocarditis is first discovered as a result of the search for the cause of such hematuria. However, hematuria in subacute bacterial endocarditis may also be due to large infarction of the kidney or to diffuse glomerulonephritis. As mentioned above, in such a patient sudden, copious hematuria, usually accompanied by pain in the side or back, points to the existence of a large infarct. Christian's[57] findings indicate that large numbers of erythrocytes in the sediment are more apt to be due to glomerulonephritis than to focal glomerular lesions Diffuse glomerulonephritis is rare in the active stage of the disease, but decidedly more common in Libman's bacteria-free stage; in fact, Libman states that it is fifteen times as frequent in the latter period of the disease. The presence of edema (not due to myocardial failure or to hypoalbuminemia in cachectic patients) or hypertension in subacute bacterial endocarditis indicates the existence of diffuse glomerulonephritis. The same is true, apart from the rare exceptions just mentioned, of impairment of renal function However, diffuse glomerulonephritis often occurs in subacute bacterial endocarditis in the absence of hypertension, edema and impairment of renal function; in such cases, hematuria due to the diffuse lesion cannot be differentiated from that produced by focal glomerular lesions. It should be remembered, in this connection, that diffuse glomerulonephritis and focal glomerular lesions are often found in the same kidney.

Prognosis and Treatment.—The prognosis and treatment are those of subacute bacterial endocarditis, not being influenced by the presence of focal glomerular lesions. In particular, the presence of focal renal lesions s' ... il the attempt to give the patient the ample nour- ... fat
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lesions are hardly found.

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Chapter

24

ESSENTIAL HYPERTENSION. I. CONCEPT AND PATHOLOGICAL ANATOMY

HISTORICAL DEVELOPMENT OF THE CONCEPT OF ESSENTIAL HYPERTENSION

For many years the symptom of hypertension was all but universally regarded as invariably a consequence of preexisting renal disease or arteriosclerosis It is true that there were individual observers who surmised the existence of hypertension not due to disease of the kidneys or sclerosis of t[illegible] even spoke of a "prealbuminuric stage of [illegible]

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tension was inevitable Indeed, von Basch himself, who made over 100,000 blood-pressure estimations, was very well acquainted with our present essential hypertension, which he termed "latent arteriosclerosis." In 1893, he wrote of observations which he had been making for many years "There are numerous cases in which examination reveals a high tension of the pulse, but the other characteristics of outspoken arteriosclerosis are either absent or but minimal." Von Basch viewed the stage of isolated hypertension as a precursor of arteriosclerosis; hence his term *latent arteriosclerosis*

It was not von Basch, however, but Allbutt in England and Huchard in France who, by their keen clinical observations and brilliant writings, brought the medical profession to a realization of the enormous frequency of [illegible] significant

[illegible]

sure whom he watched for eighteen years, but "years passed on and the dreaded Bright's disease never appeared," until she finally died of cerebral hemorrhage Allbutt named such cases hyperpiesia, after the predominant symptom, and brought order into the previously confused hypertension-kidney disease-arteriosclerosis group by differentiating.

1 Hyperpiesia, in which high blood pressure dominates the clinical picture, with little renal involvement.

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were termed pseudoleukemia until some of the individual diseases thus ... disease, lymphosarcoma, leukopenic leukemia,

hypertension will be revealed and this term ... beginning in this direction has already been

of essential hypertension.

PATHOLOGICAL ANATOMY OF ESSENTIAL HYPERTENSION

... from essential hyper- ... found. Less constant, ... is arteriolosclerosis of a ... degree far more pronounced than occurs in normotensives of the same

tension also have a high degree of atherosclerosis of the large arteries, but this is of course also common with normal blood pressure. Finally, in those patients in whom the blood pressure has risen to exorbitant heights with the clinical picture of malignant hypertension, arteriolar necrosis may be found. The lesions just enumerated are common to all etiologic varieties of hypertension, being conditioned principally by the duration and severity of the hypertension and the age of the patient. It is in the absence of the specific renal lesions of glomerulonephritis, pyelonephritis, glomerulosclerosis, etc., that the anatomical findings of essential hypertension differ from those of other forms of high blood pressure.

The Kidney in Essential Hypertension.—In a large majority of cases of essential hypertension, the kidneys are found at necropsy to be more or less damaged. The renal lesions of essential hypertension were formerly not differentiated from those of chronic glomerulonephritis, both being united in the concept of "chronic interstitial nephritis." However, later investigations showed conclusively that in essential hypertension the changes in the kidney are secondary to disease of the small arteries—the so-called arteriolosclerosis—and in recent years the term *arteriolosclerotic kidney* has been appropriately applied to the renal lesions found in the vast majority of cases of essential hypertension.

... differentiated ... egler[13] In the ... eriosclerosis of ... arteriosclerosis in old individuals. The arteriosclerosis of the large vessels results, through infarction, in the production of isolated large scars in the kidneys, irregularly distributed and usually not very numerous. Between these large scars,

2. Bright's disease, the true renal disease, with or without high blood pressure.

3. Decrescent arteriosclerosis, the senile atheroma of the large arteries, not necessarily associated with high blood pressure.

Almost simultaneously with Allbutt, Huchard recognized the frequency of non-nephritic hypertension. He wrote: "Arterial hypertension is the *cause* of arteriosclerosis; it precedes by a longer or shorter time the evolution of the various diseases (arterial cardiopathies and nephritides) which are themselves dependent on the vascular sclerosis." To emphasize the fact that the hypertension antedates the sclerotic changes in the vessels and kidney, he termed the condition "presclerosis."

In this country the disease—doubtless more accurately diseases—was first extensively studied by Janeway,[5] and next by Moschcowitz,[6] Christian,[7] O'Hare,[8] Keith, Wagener and Kernohan,[9] Bell and Clawson,[10] and many others.

At present this disease—the prealbuminuric stage of chronic Bright's disease of Mahomed, the latent arteriosclerosis of von Basch, the hyperpiesia of Allbutt, the presclerosis of Huchard, the hypertensive cardiovascular disease of Janeway, the benign and malignant sclerosis of Volhard and Fahr[11]—is most widely known in this country as *essential hypertension*, a term introduced by Frank[12] (*essentielle Hypertonie*, really essential hypertonia).

*The concept of essential hypertension includes those patients with high blood pressure in whom none of the known causes (listed on page 272) of clinical hypertension is demonstrably operative.** *The concept is thus a negative one* and the definition is very seriously defective, in that it defines solely by exclusion, but in our present ignorance of the actual etiology, it does not seem feasible to define essential hypertension in any more satisfactory way. *The very term essential hypertension is a confession of ignorance—and this is its chief virtue.* The noun expresses the dominant clinical manifestation and the adjective serves the double function of forewarning of our ignorance of the cause of the hypertension and differentiating it from nephritic hypertension. All that the term essential hypertension really means is hypertension of unelucidated origin. But it is a very necessary term, for the hypertensions of unknown origin are far more frequent than those due to nephritis, suprarenal tumor or other known causation. The concept of essential hypertension is merely a stop-gap necessitated by our present ignorance. It seems highly probable, in fact almost certain, that essential hypertension is merely a collective concept (a *Sammelbegriff*, as the Germans would say) for a number of conditions having in common the positive characteristic of arterial hypertension and the negative one of the absence of known causation. The situation is analogous to that which formerly obtained in the group of diseases characterized by generalized enlargement of the lymph glands in the absence of a leukemic blood picture. These

* ... inflammation of the kidneys, obstruction along the urinary tract, pheochromocytoma or other known cause.

arteriosclerotic or other narrowing of the main trunk or first branches of the renal arteries in the cases of essential hypertension without renal arteriolar sclerosis. Moritz and Oldt[19] have reported 3 such cases (see also page 699). However, such cases are extremely rare, the only unequivocal instance that has come under my observation is one in which hypertension set in acutely and operation revealed thrombotic occlusion of a sclerotic renal artery.

Older knowledge of the morphology of the renal vessels in hypertension was derived from post-mortem studies. New light has been thrown on the subject by the *intra vitam* observations of Castleman and Smithwick.[20] During sympathectomy on hypertensive patients, they removed a segment of the renal cortex 6×5×4 mm. in size and containing about 50 cross sections of arterioles and small arteries. In 500 cases they found that these small vessels revealed no pathological changes in 4 per cent, mild alterations

by present histologic technique

the kidney specimens are large enough to give an accurate index of the

Changes in the renal vessels and kidneys may be practically absent when hypertension results from suprarenal tumor or basophilic adenoma In the case of suprarenal tumor with great hypertension (heart weight, 880 grams) reported by Oppenheimer and the author,[22] the renal changes were minimal, and the same has been true in other similar cases in the literature

THE ARTERIOLOSCLEROTIC KIDNEY —As was mentioned above, such cases of essential hypertension without renal lesions discoverable at necropsy are decidedly exceptional. Much more commonly, one encounters kidneys in which microscopic examination reveals well-marked arteriolosclerosis and foci of atrophy of the parenchyma, despite the fact that macroscopically there is no evidence of disease. The surface is smooth, and there is no contraction, the consistency is often somewhat increased or even this may be normal Not uncommonly, in fact, such kidneys are slightly enlarged as a result of chronic passive congestion, for cardiac failure is the most common cause of death in essential hypertension. Such instances, in which the kidneys appear normal to the naked eye, but reveal definite arteriolosclerotic lesions on microscopic examination, are particularly common in relatively young individuals who have succumbed to

of renal damage is immediately evident at the necropsy, the arteriolosclerotic kidney is found. It presents the following characteristics: Usu-

the kidney surface is smooth and microscopic examination reveals large areas of intact parenchyma. Sometimes, however, the scars are greater in number and by their intersection produce a coarse pseudogranulation. In such instances, the kidney may be considerably contracted. There may be large, flat, sunken areas, corresponding to the closure of particularly large branches. The picture differs notably from the more finely granular appearance of the well-developed arteriolosclerotic kidney.

The arteriosclerotic kidney is usually of little clinical significance. Apart from the rare instances mentioned on page 677, it is not accompanied by hypertension, and, while it may cause slight proteinuria, disturbances of renal function are rarely if ever serious. It is the most common anatomical substratum of the so-called senile kidney. Of course, arteriosclerotic and arteriolosclerotic changes are not uncommonly associated in the same kidney.

Essential hypertension is a disease which usually lasts for many years or even three or four decades before death occurs, either as a result of the disease or some independent malady. During this period, the renal damage progresses at a varying rate, so it is not surprising that the state of the kidneys as encountered at necropsy varies within wide limits. In some instances, the renal damage is minimal, but there are also all gradations down to extremely contracted kidneys as small as those encountered in chronic glomerulonephritis of many years' duration.

Essential Hypertension with Intact Kidneys.—It is decidedly unusual for a case of essential hypertension to come to necropsy without well marked renal arteriolosclerosis being found. As mentioned above, I did not encounter such an instance in 72 cases of essential hypertension which I studied anatomically. However, the study was at Montefiore Hospital for Chronic Diseases and all of the cases had had very protracted clinical illnesses. Since then I have seen several necropsies in which marked hypertension had been present and yet the state of the renal arterioles and small arteries was not abnormal for the age In one of them the blood pressure had been continuously over 200 mm. systolic and 100 mm. diastolic for at least three years, and probably for a considerable time longer

Cases of essential hypertension in which the kidneys were found normal at necropsy were long ago reported by Pal,[14] von Monakow,[15] Kauffmann,[16] and others. Bell and Clawson, in fact, found no arteriolosclerosis in 10 per cent of their cases of essential hypertension, but they consider as arteriolosclerosis only lesions of the vasa afferentia, not including changes in the interlobular vessels Wallgren[17] had 8 cases of essential hypertension in which the renal arterioles showed no changes other than those corresponding to the age of the individuals. In one of Kauffmann's cases with normal kidneys and no arteriolosclerosis, the patient was known to have had hypertension for twelve years. In his most recent studies, Bell[18] finds that at necropsy 17.5 per cent of patients with essential hypertension but no renal insufficiency have renal arterioles and prearterioles which he regards as normal.

The foregoing data refer to the minute intrarenal arterial vessels.

In the light of the experimental production of hypertension by constriction of the renal artery, the question comes up whether or not there was

areas. Sometimes, the granules have a yellowish tone, so that the kidney as a whole appears paler, resembling a secondary contracted kidney. Small cysts are often present.

The kidney substance is tough and hard. It offers a considerable resistance to the knife On section, it is seen that the cortex is greatly thinned, the medullary pyramids less so, and the borders between cortex and medulla are often not clearly defined. The cortical markings are [illegible] areas may be seen descending from the [illegible]. In the [illegible] only ab- [illegible] normality noted The arteries are rigid, have thickened walls, and gape.

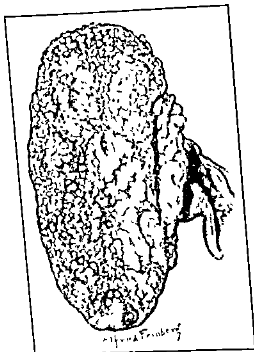


Fig 41 —Late stage of the arteriolosclerotic kidney of essential hypertension (primary contracted kidney) Striking granulation and marked contraction

Histology of the Arteriolosclerotic Kidney —Microscopically, the picture varies with the stage of the process In cases which have died at an early phase (for example, of cerebral hemorrhage), there may be only arteriolosclerosis, while the renal parenchyma is intact or there are a few hyaline glomeruli The next stage is represented by the formation of small foci of atrophy of the parenchyma separated by large areas of intact kidney substance These atrophic foci are most commonly situated at the [illegible] surface Often, [illegible] supply, they are [illegible] In these areas,

ally the capsule is adherent, often so firmly that there is considerable laceration of the kidney substance as the capsule is stripped. In other instances, the capsule comes off readily despite the presence of contraction and granulation. If the kidney is contracted, there is an increase in the fatty capsule and the adipose tissue in the hilus. The size of the kidneys varies greatly; they may be somewhat enlarged through congestion or of normal size, but more often there is contraction of varying degree. Rather rarely, extremely small kidneys rivalling the secondary contracted kidney of glomerulonephritis are encountered. As a rule, however, the amount of contraction is less than in the secondary contracted kidney.



FIG 40 — The arteriolosclerotic kidney of essential hypertension Granulation and moderate contraction, two cysts

The surface is granular The granules are usually both fine and coarse and often irregularly distributed. Sometimes there is a uniform fine granulation. In other instances, there is considerable contraction with little granulation, the surface being but slightly irregular The granules correspond to areas of relatively intact or even hypertrophic parenchyma, the intervening indentations to atrophic and scarred areas. There may also be large scars due to arteriosclerosis of the large vessels. The general color of the surface is usually a brownish or grayish-red (red granular kidney), the granules being mostly lighter in color than the intervening

an early feature of the glomerular process is a thickening and wrinkling of the basement membrane of the glomerular capillaries, which is accompanied by a decrease in size of the glomerulus and a simplification of its structure. As the arteriolosclerosis progresses and further narrows the lumen of the interlobular or afferent arteriole, collapse and hyalinization of the capillaries of the appertaining glomerulus occur. All the capillaries of a glomerulus may be simultaneously involved or only some become

At the border of hyaline areas

nuclear proliferation, but gener-

the glomeruli and other inflammatory reactions, such as occur in glomerulonephritis and less diffusely in the malignant phase of essential hypertension, are either absent or are found in but a very small percentage of the glomeruli (Klemperer and

Finally the individual hyaline areas fuse. The

hyaline sphere

centric layers of connective tissue around the parietal layer

occur despite the fact that the tuft of the Malpighian corpuscle is little altered, so that the latter is seemingly obliterated by the compression of

ion of the tuft and

the hyaline sphere

of the tuft is readily distinguished from the concentrically thickened capsule. The h

completely fibrosed and indistinguishabl

ssue. Occasionally, calcification of

If the destruction of glomeruli is very widespread, the intact Malpighian bodies may be hypertrophic

The Tubules —The tubule belonging to an obliterated glomerulus atrophies. The epithelium becomes smaller and shows fatty and other regressive changes. Finally, there remain

of atrophy. (1) The blood supply to the tubules comes almost exclusively from the glomerulus (Gross,[27] Langley[28]), and is cut down by obliteration of the latter.* (2) The cessation of glomerular filtration probably entails a disuse atrophy of the tubular epithelium, which no longer has fluid from the glomerulus to resorb. In his microdissections of the arteriolosclerotic kidney Oliver[29] found little evidence, except in the malignant phase, of tubular obstruction by débris with consequent hydro-

by-passing the fibrosed glomeruli, bring blood directly to the tubules

the glomeruli are shrunken and hyalinized and the tubules atrophic, both being surrounded by connective tissue. In more advanced stages, these foci are more numerous and coalesce, until finally a stage is reached in which there are only isolated areas of intact parenchyma; in these, glomeruli and tubules may be hypertrophic, the latter showing evidence of regeneration.

The Glomeruli.—In most cases of essential hypertension, obliteration of glomeruli has been going on for many years by the time they come to necropsy. The result is that some fraction of the totality of glomeruli has already been completely destroyed, while others are in various stages of

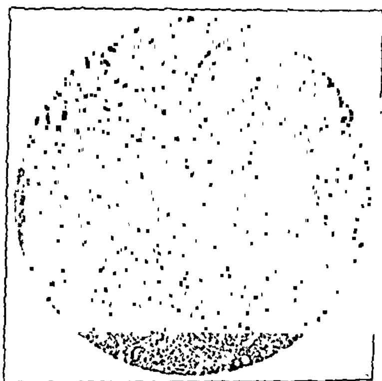


FIG 42.—Hyalinization of glomeruli in the arteriolosclerotic kidney of essential hypertension; secondary degenerative changes in tubules (Same kidney as Figure 4, page 285.)

the process, and still others are completely intact. As a rule, fewer intermediary pictures are seen than in most instances of glomerulonephritis or the malignant phase of essential hypertension, in which the patient is apt to succumb while g

The glomerular

follow the latter.*

Sometimes one
al portion of the
omeruli should be
Cont-

... the same changes as in the benign

... f

tension is, ... e acute arteriolar lesions is the renal arterioles. ... discussed on page 825. The necrotizing and endarteritic process involves the afferent and interlobular arterioles and may extend into the glomerulus.

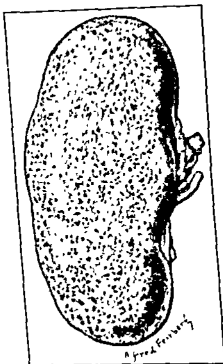


Fig. 43 —Kidney in the malignant phase of essential hypertension Numerous hemorrhages of varying size, surface almost smooth

Not all the arterioles are thus affected, but sometimes the process is very widespread The necrotic areas of the walls of the affected vessels are swollen and stain a deeper red with eosin than does an area of hyaline degeneration, often they appear "smudgy" The *necrotic substance* is often distinctly granular In it, the nuclei have either completely disap- ... Both ... vessel ... aracter-istic appearance is often seen when the vas afferens is necrotic at its entrance into the glomerulus, appearing in the hematoxylin-eosin preparation

nephrotic distortion. The tubules in intact areas become hypertrophic and show evidences of

has been very great.

the proximal convoluted tubule. In those cases which had impairment of renal function, there are areas of greatly dilated tubules [illegible]ed by low

e been de-

However, the compensatory hypertrophic changes are rarely as well marked in essential hypertension as in glomerulonephritis. The reason for this is probably that only a comparatively small proportion of cases of essential hypertension develops renal insufficiency, so that compensation by intact elements is not needed; also, in essential hypertension the blood supply to even the intact parts is notably diminished by the arteriolar disease.

As the specific renal elements atrophy, there occurs a replacement fibrosis which in some long-standing cases becomes very widespread. Round-cell infiltrates are not uncommonly present in the interstitial connective tissue. Rather exceptionally, there is considerable deposition of lipoid in the medullary portions.

The lesions of the afferent and interlobular arterioles, which initiate the renal changes, have already been described (page 284) McGregor[24] found in serial sections that the efferent arterioles are normal. However, I have repeatedly observed that in patients with both hypertension and diabetes there may be high-grade hyalinization of the efferent arterioles.

Anatomical Findings in the Malignant Phase of Essential Hypertension.—There are very characteristic lesions in the malignant phase of essential hypertension These were first described by Fahr,[30] and since then important contributions have been made by Herxheimer,[26] Stern,[31] Keith, Wagener and Kernohan,[9] Bell and Clawson,[10] Murphy and Grill,[32] and Klemperer and Otani. The lesions have been exhaustively studied by Dr. Paul Klemperer at Mount Sinai Hospital. In two years, he encountered 12 typical cases at necropsy Through his kindness, I have been enabled to study the anatomical preparations of these cases as well as many in subsequent years

The macroscopic picture of the kidneys is often so characteristic that in most cases, inspection renders one strongly suspicious of the nature of the histological process before seeing the sections The kidneys are generally of normal size or even somewhat swollen, but in other cases there is considerable contraction. The surface may be but slightly granular or the granulations may be well marked Evidently, both the size and the amount of granulation depend on the duration of the "benign period" preceding the malignant phase. The fundamental color is generally the brownish or grayish-red found in the usual case of essential hypertension, but, in addition, the color is variegated by the presence of yellowish areas and of hemorrhages. The latter are often very numerous, of varying size, and frequently of irregular outline. Such hemorrhages are extremely uncommon in ordinary essential hypertension and constitute, when present in large number, the characteristic macroscopic feature of the malignant phase of the disease. But they are not present in all instances.

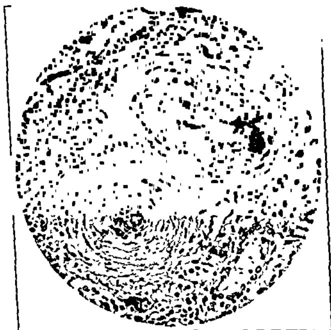


FIG 45 — Two small arteries of kidney in the malignant phase of essential hypertension The upper vessel shows arteriolar necrosis, the lower endarteritis with endothelial proliferation

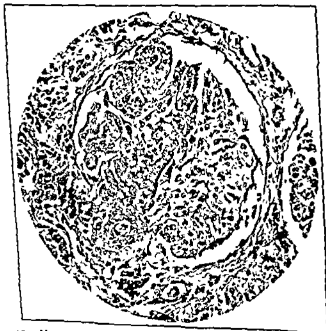


FIG 46 — Necrosis of the vas afferens and its first branches in the malignant phase of essential hypertension.

as a deeply red-stained ring which stands out prominently. The first divisions of the vas afferens may also be *necrotic*. Thrombosis of the involved vessels is very common.

In most, if not all, of the cases there is also well-marked endarteritis of the small renal arteries and arterioles. It *may attain an extreme degree.* It consists in connective-tissue thickening of the intima; endothelial proliferation is *frequently well marked.* There may also be periarterial cellular infiltration, *this is quite probably* a reaction to the regressive changes in the inner layers of the vessel wall (Klemperer). Fatty change

Fig. 44.—Kidney in the malignant phase of essential hypertension. Fewer hemorrhages than in kidney of Figure 42, marked granulation

may occur in the wall of the affected vessel, but Herxheimer[26] states that this sclerosis. Blood may surrounding tissues,

Some of the glomeruli are atrophic or hyaline as in the benign form of essential hypertension, though these lesions are often not widespread. In addition, there are changes which resemble those of glomerulonephritis but are not diffuse. These consist in moderate proliferation of the nuclei of the tuft as well as of the capsular epithelium. It is to be emphasized that they involve only a portion of the glomeruli, usually only a small

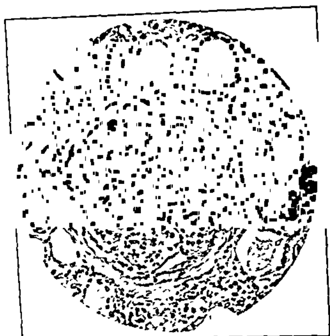


FIG 47 —Necrosis of some glomerular loops in the malignant phase of essential hypertension

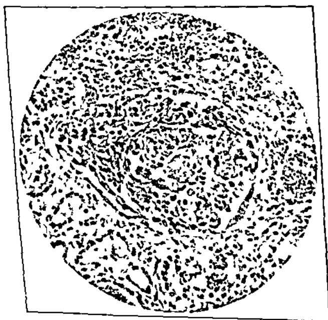


FIG. 48 —Proliferation of epithelium of glomerular capsule with crescent formation in the malignant phase of essential hypertension.

percentage. Some of the glomeruli show necroses. Most often the necrosis is confined to the first branches of the vas afferens, being continuous with the necrotizing process in the wall of this vessel. In other instances, the entire glomerular tuft is necrotic with nuclear fragmentation. The cause of such necrosis *in toto* of the glomerulus can sometimes be demonstrated to be thrombosis of the afferent arteriole. There is often hemorrhage into the capsular space from a necrotic capillary loop.

The tubules present the same atrophic and degenerative changes as in the benign forms of essential hypertension In the malignant phase of the disease, however, owing to the rapidity of the process, the degenerative changes in the tubular epithelium are generally much more striking. Hyaline-droplet degeneration may be especially prominent. The tubules often contain blood.

In the cases of the malignant phase of essential hypertension that I have seen, arteriolar necrosis has occurred, though not commonly, in organs other than the kidney. Among these organs have been the intestine, suprarenal gland, pancreas, and liver, but in each instance only isolated vessels have been affected. Cohen[34] has observed chorioretinal arteriolar necrosis. Klemperer has found endarteritis in a number of cases of the malignant form of essential hypertension in the liver, pancreas and other organs Endarteritis seems to be generally, if not always, present in the small arterial vessels of the retina and choroid when there is hypertensive neuroretinopathy in these cases. (See illustrations of Keith, Wagener, and Kernohan [9]) It was mentioned above that Kernohan, Anderson and Keith have found medial hypertrophy in the arterioles of the voluntary muscles in the malignant phase of essential hypertension Necrosis and endarteritis of arterioles or small arteries may produce ischemic lesions in the bowel, pancreas, brain and other organs; I have seen intestinal perforation of this organ and Hranilovich and Baggenstoss[35] observed pancreatic infarcts in 7 and pancreatic focal necrosis in 21 of 100 patients with malignant hypertension.

Other Anatomical Findings in Essential Hypertension.—While cardiac hypertrophy, arteriolosclerosis and the arteriolosclerotic kidney are the lesions most constantly encountered at the necropsy of an individual who had essential hypertension, other changes are almost invariably also present These, however, vary greatly in different instances

Arteriosclerosis of the large arteries is present in the vast majority of instances, often in a widespread and severe form. This is particularly the case where the hypertension is associated with diabetes or occurs in very old individuals. The consequences of such arteriosclerosis of the coronary or cerebral vessels quite often dominate the clinical picture, in such instances, myocardial degeneration or areas of softening in the brain are found. Or the combination of the hypertension and cerebral vascular disease may have led to cerebral hemorrhage. Arteriosclerotic changes in the choroid and retina are common. There is generally well-marked or severe arteriosclerosis of the aorta and its branches, but in other cases these vessels show little more atheromatous change than is usual at the age of the patient. Arteriosclerotic gangrene of the extremities is rare except if the hypertension is complicated by diabetes. Arteriosclerotic lesions of

predisposes to essential hypertension. Another belief that has ... considerable currency is that essential hypertension is more common ... professional classes than among the poor. It

Certainly, if worry and other forms of emotional strain are ... factors in the genesis of essential hypertension, this class of poor women should have its full share and more of the disease. In the next paragraph ... that urban negroes, whose whole life is a struggle ... *et al.* ... poor ... former.

RACE AND ESSENTIAL HYPERTENSION

Race is apparently a factor that influences the incidence of essential hypertension. From the scanty information available, the latter appears to differ among various peoples. However, it has not been established that the differences in incidence of essential hypertension between ethnic

found that essential hypertension is rare among Chinese and other oriental peoples who normally have a lower blood pressure than occidental Cau-

Cuni and Zuni Indians. Kean's[8] careful studies reveal that in Panama the West Indian negroes have a higher normal blood pressure than the Panamanians and about seven times as high an incidence of hypertension. Among Indians in the Southwest of the United States, who live largely a reservation existence, Cohn[9] observed the incidence of hypertension to be

tered only two questionable instances among them. Contrariwise, essential hypertension is very common in negroes living in large cities in the

Chapter

25

ESSENTIAL HYPERTENSION. II. ETIOLOGY AND PATHOGENESIS

The nature and causation of essential hypertension have been the object of a great number of clinical, post-mortem, experimental and genetic studies ever since the frequency of the disorder—rivaled only by arteriosclerosis, which it so often overlaps, among lethal maladies—became clear early in this century. With the experimental production of hypertension by Goldblatt, the tempo of investigation became accelerated. Many facts have been established and a number of theories based on accurate observation and experimentation propounded. Nevertheless, *neither the cause nor the nature of essential hypertension are understood.* Indeed, what is labeled essential hypertension doubtless includes more than one nosologic entity. *The immediate mechanism of the rise in blood pressure is augmented contraction of the arterioles.* But what increases the contraction of the arterioles in essential hypertension remains a mystery. At present, theories regarding essential hypertension as primarily a psychosomatic disorder, an aberration of the endocrine glands, or a consequence of renal arteriolar sclerosis or other kidney disease hold the center of the stage. The possibility exists that each of these explanations may hold in still undifferentiated conditions grouped under essential hypertension, and they may not be mutually exclusive. *But as yet none of the conceptions of the nature of essential hypertension is more than a theory, perhaps not more than a working hypothesis.*

THE FREQUENCY OF ESSENTIAL HYPERTENSION

Essential hypertension and its consequences are among the most common conditions confronting the practitioner. Among 7,872 private patients, Janeway[1] found that 870, or 11.1 per cent, had systolic blood pressures of 165 mm. or more, the large majority being instances of essential hypertension. In Romberg's[2] private practice, 24.8 per cent of all organic heart disorders were due to hypertension. Fahr[3] calculates that 140,000 deaths in the United States in 1924 were due to hypertension or its consequences, this being 23 per cent of all deaths in persons over fifty years of age. Bell's[4] autopsy findings indicate that about 13 per cent of individuals past fifty years die of hypertensive disease. These figures afford some indication of the importance of essential hypertension to the physician, a fact which has been adequately realized only within recent years.

Essential hypertension is far more frequent than nephritic hypertension. Of 82 instances of hypertension which I studied at necropsy, 72 were essential and only 10 nephritic. On Romberg's service there were 656

AGE AND ESSENTIAL HYPERTENSION

Essential hypertension only exceptionally produces symptoms before the declining phase of life. To how early an age its roots extend will be discussed below, but it is certain that in the vast majority of instances the clinical manifestations of the disease first appear after the age of forty years Janeway[1] found that the three decades from forty to sixty-nine
1

s of thirty and forty
ertension during this
of cases of essential
military and routine
examinations, but it is rare for the disease to produce symptoms at this time of life unless they are engendered by fear of high blood pressure. However, even in early childhood there are rare cases of essential hypertension which produce symptoms and even prove fatal Above was mentioned a case of essential hypertension which went into the malignant phase and succumbed at the age of eight and a half years. Holzmann[21] has described essential hypertension in a boy aged four and a half years. Hutchison and Moncrieff[22] observed a boy, aged eight and a half years, whose blood pressure was 210/150 mm , at necropsy, the kidneys were found normal. So far as I am aware, the youngest sufferer from essential hypertension on record is the colored boy, aged two years, reported by Taussig and Remsen[23] with a blood pressure of 195/135 mm., at necropsy the kidney showed but slight changes Sobel[24] found in the literature slightly less than 100 cases of essential hypertension in children and reported 7 of his own However, these were probably not all cases of essential hypertension, Sobel's first case had precocious puberty and may have had disease of the adrenal cortex

The following table gives the age and sex incidence of 96 cases of chronic hypertension which were shown at necropsy not to be due to glomerulonephritis or pyelonephritis

Age at death, years	*Number of cases*	
	Male	*Female*
0 to 29	2	0
30 to 39	2	4
40 to 49	5	14
50 to 59	18	16
60 to 69	10	14
70 to 79	3	6
80 to 89	1	0
91 to 99	0	1
Total	41	55

United States. In New York City, I have obser

... found

... more than twice as common in negro factory workers than in their white companions. Flaxman[14] noted in Chicago that hypertensive heart disease is more common in negroes (I have also observed that the proportion of cases of essential hypertension in which the clinical picture is dominated by heart failure—not angina—is higher in colored patients, perhaps because of their strenuous occupations). According to Weiss and Prumack,[15] hypertension tends to occur earlier in the negro. In another group of negroes residing in the midst of "civilization," the South African Bantus, Ordman[17] found a high incidence of hypertension. Dubois[16] observed systolic hypertension (he measured only the systolic pressure) in the Congo; I do not know the state of their culture or their relations to the Caucasian settlers.

Blackford[18] quotes Firestone as finding that the Eskimos have approximately the same incidence of hypertension as occurs in the United States.

In New York City I have found that essential hypertension is more common in Jews of the poorer groups than among Gentiles of corresponding economic status, but have not noted such a difference among the well-to-do. I have observed that the ratio of essential to nephritic hypertension is much higher among Jews than among Gentiles; this difference is also due to the lower incidence of glomerulonephritis among Jewish than other, es

... rates is not at hand. Genetic factors, differences in occupation, diet and mode of life are among the factors that must be taken into consideration. Further study of comparative pathology is highly desirable in the hope that it may throw light on the importance of genetic factors in hypertension, and perhaps elucidate the importance of diet, of psychosomatic influences, and of a so-called "civilized" environment in producing high blood pressure. If it is proved that the incidence of essential hypertension rises with civilization, the problem then arises of unveiling whether it is the diet, complicated interpersonal relationships, or other aspects of our way of life that is guilty. The explanation of why the negro in his primitive environment in Africa has little hypertension while it is among the most common afflictions of the American negro may well be a clue to the nature of essential hypertension.

An excellent bibliograph
different races is given by
racial differences do exist,
entiate the importance of genetic, psychologic and social factors (the authors, it seems to me, overestimate the importance of the influence of arm size in determining racial differences).

Climate.—More information is needed regarding the relation of climate to essential hypertension. Some evidence that tropical climate tends to lower normal blood pressure is cited on page 267. I have the impression, without supporting statistical evidence, that essential hypertension is not as enormously frequent among whites in the far South of the United States

SEX AND ESSENTIAL HYPERTENSION

Essential hypertension is a common disease in both sexes. There have been differences of opinion whether essential hypertension is more common among males or females because few series include all types of clinical

hypertension following the menopause. Bell and Clawson found essential hypertension 1.4 times as common in males. On the other hand, two-thirds of Boas and Fineberg's[29] 236 cases of essential hypertension were in women. Blackford, Bowers and Baker[30] also found hypertension twice as often in females. In dispensary practice I have also observed essential

males and 11.9 per cent in females. To the writer it seems that the reason for the greater clinical incidence of hypertension in females is that the disease lasts longer in them, especially because of the smaller incidence of coronary disease.

HEREDITY AND CONSTITUTION IN ESSENTIAL HYPERTENSION

Heredity.—It was already known to Morgagni[32] that there is a marked predisposition in certain families to cerebral hemorrhage, which is in the vast majority of instances
stration of the hereditary
is rendered more difficult
clinically manifest in middle or late life, so that the parents and many other relatives of the patient are not available for examination. It is probably for this reason that Janeway underestimated the significance of heredity in essential hypertension.

many individual
the hereditary
there is a marked tendency for the disease to occur not only in successive generations but also in several brothers and sisters of a single generation. Thus, Rosenbloom[33] observed a family in which both parents died of cerebral hemorrhage, of their 10 children, 8 already have hypertension, only the 2 youngest (aged thirty-three and thirty-five years) not as yet having any elevation of blood pressure. Allbutt[34] mentions a man with hypertension whose paternal ancestors for three generations died of cerebral hemorrhage, a total of four generations. Nikitis[35] was able to trace the predisposition to arterial hypertension through three generations of the f

per cent of 451 controls. Most practitioners are acquainted with families the members of which are subject to "strokes."

The cases under thirty years of age were in a man, aged twenty-three years, with a tumor of the suprarenal cortex and in a youth aged sixteen years with hypothyroidism. In this series there were thus no cases of essential hypertension which proved fatal before the age of thirty. The table indicates that eighty per cent of fatalities in patients with essential hypertension occur between the ages of forty and sixty-nine.

The above figures refer to the clinical incidence of essential hypertension, *i. e.*, to individuals whose blood pressure is measured when they come to the physician or hospital because of illness. In recent years, however, measurements of the blood pressure of those who believe themselves healthy have made it evident that *the roots of the disease extend to a much younger period of life.* The enormous number of blood pressure determinations carried out nowadays on seemingly healthy persons in conjunction with military service, insurance, industrial employment, college admission, etc., disclose that a higher proportion than was previously realized have a blood pressure above the normal for the age. Alvarez[25] found that 20.7 per cent of seemingly healthy male college students and 2.7 per cent of female students have a systolic pressure above 140 mm. In a similar investigation, Diehl and Sutherland[26] showed that a large proportion of these elevations are transitory, being due largely to the emotional impact of the examination. These authors found an incidence of 5.6 per cent of permanent or transitory [illegible] only under the emotional stress of an insurance or military examination and followed by repeated normal readings when the patient became accustomed to the examiner. However, the writer has for many years been convinced that *at least the larger moiety of* [illegible] *tional" hypertension ultimately* [illegible] it may be decades before this is [illegible]. For example, the author recently saw a man of thirty-nine years who was considered to have developed essential hypertension only within the past year, but who gave the information that when his mother consulted a famous student of hypertension for essential hypertension thirty years before, this clinician had measured his blood pressure and predicted that some day he would have his mother's disease. The history is often given by patients with essential hypertension that when they were young—in the 'teens or twenties—an examiner had been suspicious of high blood pressure but had failed to confirm his suspicion on subsequent examinations. In a study of the medical records of over 22,000 Army officers, Levy[27] *et al.* found that sustained hypertension developed more frequently in those who previously had transitory hypertension. And Hines[28] showed that individuals whose blood pressure is in the upper range of normal often show manifest essential hypertension ten or twenty years later, while this rarely develops in those with low normal pressures. Early appearance, often in the 'teens, of the precursory manifestations of essential hypertension is especially apt to be found when both parents are hypertensive. All these observations indicate that the actual onset of essential hypertension occurs long before the disease becomes manifest (*cf.* also page 758).

The hereditary factor in essential hypertension was first exhaustively studied by Weitz.[37] He found that among 82 patients with essential hypertension, 63 or 7 ... at least one parent from consequences of hypertens ... seemed probable in 1 ... 3 In only 6 of the 8 ... ntrols only 30.3 per cent had ...

... both of whom ... hard life working in a ... As a result of his investigations, Weitz concludes that essential hypertension is inherited as a dominant characteristic, though he admits that the dominance is not invariably demonstrable Hines[38] likewise adduced evidence that essential hypertension is inherited as a dominant characteristic. He found that a family history of hypertension is five times as frequent among hypertensives as among controls In a careful study, Ayman[39] found that in families in which both parents had normal blood pressure only 3.1 per ... had high blood pressure, while the latter was present in

...

hypertension is inherited as a Mendelian dominant. ... indicate the same

Investigations on *twins* have also brought evidence of the importance of a genetic factor in essential hypertension From his survey of 31 pairs of monozygotic twins with hypertension, Sobye finds that concordance occurs so often in proportion to discordance as to argue strongly for a hereditary factor

Now that determination of the blood pressure had been a routine part of the usual medical examination for over thirty years, the writer has had frequent opportunities to obtain evidence regarding the blood pressure of the siblings, parents and even grandparents of hypertensive patients. The data thus obtained, as well as the literature above summarized, have convinced me that *no fact relevant to the nature of essential hypertension is as well established as the fundamental importance of heredity*

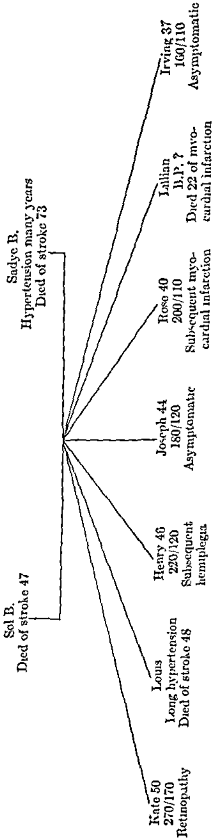
Parenthetically, it may be remarked that arterial hypotension, like

...

common

Constitutional Peculiarities.—In view of the strong hereditary element in essential hypertension, considerable attention has been paid in recent

I observed almost all the members of the following family:



For excellent discussion of the constitutional and hereditary aspects of essential hypertension, the reader is referred to the studies of Williams and Sobye[49]

THE RÔLE OF THE KIDNEY IN ESSENTIAL HYPERTENSION

Ever since Richard Bright pointed out that disease of the kidney may bring cardiac hypertrophy in its wake, there have been those who regard all persistent high blood pressure as renal in origin But when the clinical picture now known as essential hypertension was split off from the other forms of Bright's disease, many veered to the conception that this variety of elevation in arterial pressure is not caused by renal disease. This opinion, for it was no more, was largely founded on the observation that
... high blood pressure despite negative urine and a
... function. It was not based on ana-
... ly post mortem morphological data
available at the time (say ... generally interpreted to indicate
the presence of an abnorma...
all chronic hypertensives ...
10) published his experimental
constriction of the renal artery, ...
is of renal or nonrenal origin appeared to many ...
the former

Considerations Favoring the Renal Origin of Essential Hypertension. - 1 There is indubitable clinical and experimental proof that disease of the kidneys can produce chronic hypertension (Chapter 10)

2 While patients with essential hypertension start with negative urine and faultless kidney function, most of them ultimately develop proteinuria and many impairment of renal function, perhaps 7 per cent succumb to uremia

3 The first measurements of renal blood flow in essential hypertension revealed decreased flow in most of the cases (Goldring[51] *et al*)

4 The large majority of patients with essential hypertension reveal at necropsy well marked renal arteriolosclerosis And in some of the cases in which the small vessels are not sclerotic, narrowing of the main renal arteries has been observed (Blackman[52])

5 By means of his clamp, Goldblatt produced in dogs and other animals hypertension without change in the urine or impairment of renal function Such hypertension with normal urine and kidney function seemed to be a precise reproduction of human essential hypertension. Moreover, in simulation of the chronicity of the human disease, Goldblatt maintained
... years,
... ito the
... in the

The foregoing obviously constitutes strong clinical and experimental support for the doctrine of the renal origin of essential hypertension. The thesis is still maintained vigorously and ably by Goldblatt and others.

that the blood pressure is on an average higher in healthy factory workers of sthenic bodily habitus than in those of asthenic build. Similarly, most patients with essential hypertension are of a distinctly sthenic bodily habitus. They have a heavy skeletal framework, originally a good musculature, though this is often undeveloped because of a sedentary life, a broad and deep chest and a marked tendency to obesity—for which
have been described .
monly (in 71 per cent
are short and stocky w
son and Brucer[46] reveal that individuals of broad (sthenic, pyknic) body build are much more susceptible to essential hypertension than are those of linear (asthenic, leptosomic) habitus. They separated the two groups for statistical analysis by the ratio of the circumference of the chest to the height. They found that men of broad body build have more than four times the incidence of systolic hypertension and seven times the incidence of diastolic hypertension than do those of slender constitution. Robinson and Brucer observed that women of sthenic habitus had 11 times the incidence of systolic hypertension and eight times that of diastolic hypertension.

Patients of sthenic bodily habitus are

common in persons of asthenic habitus. However, one does occasionally encounter essential hypertension (proved at necropsy) in women of frail, asthenic body build

Essential hypertension is very apt to be accompanied by obesity or diabetes or both. Very often, other members of the family of hypertensive patients suffer from these disorders. In countries in which gout is prevalent, this disease is frequently found either in the hypertensive patient or his family On the other hand, tuberculosis is decidedly less frequent in those with essential hypertension than in the general population (Maurice Fishberg[47]) And when hypertension and tuberculosis are associated, the latter disease is generally of the fibroid type with little tendency to progression Apparently, the constitutional type which is predisposed to essential hypertension is relatively immune to tuberculosis.

Other constitutional peculiarities of individuals with essential hypertension have been described Thus, the investigation of Wiechmann and Pal[48] on the blood groups of individuals with essential hypertension revealed a relative predominance of groups 3 and 4. Backer[49] states that hypertension is rare in individuals with spontaneously appearing hernias, a condition which he considers indicative of low "tone" of the mesodermal tissues And Quinan[50] found that hypertension occurs with greater relative frequency in left-handed than in right-handed persons Should these investigations be confirmed, they may open up an interesting line of investigation of the constitutional variant which is unquestionably important in the genesis of many instances of essential hypertension.

Peculiarities in the psychic characteristics of some individuals with essential hypertension will be discussed below.

rather, in better accord with the view that renal arteriolar sclerosis is a process that develops with advancing age in many normotensives (page 288) but is enormously accelerated and intensified by hypertension that primarily results from another cause. But it seems plausible that as renal arteriolar sclerosis develops in the course of essential hypertension it augments the high arterial tension through whatever is the mechanism operating in the Goldblatt experiment.

Renal Pressor Mechanisms in Essential Hypertension.—There have been repeated attempts to learn whether the various pressor mechanisms studied in renal hypertension (Chapter 10) operate in essential hypertension.

Renin-Angiotonin.—There is no conclusive proof that the renin-angiotonin pressor system participates in essential or any other chronic form of hypertension, and much that speaks against it. The evidence in this regard is summarized in Chapter 10 and need not be repeated here. It may merely be reiterated that, despite repeated attempts, circulation of angiotonin has not been unequivocally demonstrated to be responsible for the elevation of blood pressure in essential hypertension.

Shorr's VEM and VDM.—Another mechanism that has recently been considered in conjunction with the pathogenesis of essential hypertension is displacement of the equilibrium between Shorr's VEM and VDM in favor of the former, which is formed in the kidney (page 331) Shorr[44] and his associates have brought forward evidence that there is a similar derangement of the VEM-VDM mechanism in essential hypertension in man and renal hypertension produced in the dog by the Goldblatt clamp In both essential hypertension and chronic experimental renal hypertension they find a balanced increase in the blood of both VEM and VDM. They showed that while normal canine and human kidneys form VEM only

kidney by the use of a tetrazolium salt which is reduced by intracellular dehydrogenases to a deep red, water-insoluble formazan They found

pattern of the red formazan deposits in the proximal convoluted tubule cells, which differs sharply from the formazan distribution in the normal tubule cell By catheterization of the hepatic and renal veins in normal and hypertensive humans, Shorr and Zweifach could demonstrate no or mere traces of VEM and VDM in normals, but in hypertensives there was a

d of VDM in the hepatic blood

ated abnormality in the VEM-

But whether this abnormality plays a part in the pathogenesis of the disease remains to be demonstrated.

However, none of the lines of evidence just sketched has proved unequivocal, and they may be countered individually as follows:

Considerations Opposing the Renal Origin of Essential Hypertension.—

1. Chronic hypertension may be produced in man by other than renal causes. This is shown by hypertension in suprarenal tumor, which is cured by ablation of the growth.

2. Many, albeit not the majority, of patients with essential hypertension have high blood pressure for a decade or more without developing proteinuria, and renal function becomes sensibly impaired in only a small proportion.

3. While the pioneer study of renal blood flow in essential hypertension by Goldring *et al.* disclosed diminution in most cases, they also obtained normal results in some instances. The same is true of the other alterations in renal hemodynamics that occur in essential hypertension (page 807) Talbott[53] and his associates compared renal clearances with biopsy findings in essential hypertension. They found that when there is little or no arteriolosclerosis, renal blood flow, glomerular filtration and the filtration fraction are normal. Only with the development of renal arteriolosclerosis do blood flow and filtration diminish. These findings are difficult to reconcile with the theory that decrease in renal blood flow is primarily responsible for essential hypertension. In his recent excellent survey of the renal circulation in essential hypertension, Chasis[54] reaches the conclusion that the alteration in renal hemodynamics is a sequel rather than the cause of essential hypertension.

4. Patients may have essential hypertension for years without demonstrable renal arteriolar sclerosis. This is shown by the biopsy studies of Smithwick and Castleman (page 677). Moreover, even necropsy material shows a not inconsiderable proportion of cases in which renal arteriolar sclerosis is no more pronounced than in many normotensive individuals of the same age (page 288). And significant narrowing of the main renal artery and its first branches is, in my experience at least, a very great rarity. That blood flow through the kidneys in essential hypertension is not always decreased by organic thickening of the arteriolar walls is also indicated by the finding of Cox and Dock[55] that postmortem perfusion of the kidney meets with little more resistance in some cases of essential hypertension than in normotensive controls of the same age. Also pointing in the same direction is the finding of Goldring *et al.* that the increase in renal blood flow in the pyrogenic reaction is of the same order of magnitude in normals and patients with essential hypertension

5. Hypertension can be produced in both humans and experimental animals by other than primarily renal mechanisms This is shown by the hypertension that may complicate the therapeutic administration of desoxycorticosterone acetate, cortisone or ACTH. It is possible that the kidney may participate in the mechanism of the hypertension, but the primary cause is the administration of the hormone.

To the writer it appears that the preponderance of evidence, as just summirized, is against the theory that the elevation of blood pressure in essential hypertension is primarily a consequence of renal arteriolar sclerosis or decrease in renal blood flow of other origin. The evidence seems,

Testing alcoholic extracts of blood and urine on cats, von [illegible] strand[67] obtained less pressor effect from hypertensive patients than from normals (cf also page 325).

Prinzmetal[68] and his coworkers and Pickering[69] attacked the problem of a circulating pressor substance in essential hypertension by transfusing blood from hypertensive subjects into individuals with normal blood pressure By cross-transfusions of as much as 2000 cc.—with the result that as much as 42 per cent of the circulating blood volume of the individual with normal blood pressure was derived from the person with hypertension—they were unable to produce rise in blood pressure. Goldman[70] and his associates observed slightly more rise in diastolic pressure when they transfused into hypertensive patients arterial blood from other hypertensives than when normotensive blood was given, but the differences do not seem significant to me

The numerous, but as yet inconclusive, attempts to demonstrate the [illegible]

renal and nonrenal hypertension a vasoconstrictor and pressor substance which they have termed *pherentasin*. They did not find it in normotensive blood The concentration of pherentasin and the diastolic pressure were not correlated The significance of pherentasin remains to be demonstrated

It is thus evident that the circulation of a pressor body in essential hypertension has not yet been demonstrated However, the available data do not rule out the presence of such a pressor substance The failure to demonstrate it in the circulating blood may be due to technical inadequacies, just as various hormones which circulate have not yet been isolated from the blood

Another hypothetical possibility that immediately comes to mind is that in essential hypertension the target organ—i e, the arterioles—is sensitized to normally circulating pressor bodies However, there is no evidence for this conception Judson[72] and his associates found no increase in the sensitivity of hypertensive patients to intravenous injections of either epinephrin or arterenol And Page and McCubbin's[73] observations indicate that the reactions to vasoactive drugs in various forms of experimental hypertension do not depend on intrinsic changes in the muscle of the vessels

The problem of intrinsic change in the arterioles in hypertensive diseases has been attacked in another way by Tobian and Binion[74] They find the sodium and water concentrations are increased in the renal artery and psoas muscle of human hypertensive subjects These investigat[illegible] also [illegible] rat. [illegible] r of [illegible] per-

It should be remembered that VEM is not itself a pressor body, but one that is demonstrated by increased vasomotion and reactivity to *epinephrin* (and perhaps sympathin or a similar substance) of certain small blood vessels in the rat's mesoappendix

The Juxtaglomerular Apparatus.—On page 336 it was seen that secretion *of a pressor body by the* juxtaglomerular cells has been suggested as the mechanism of essential and other forms of hypertension, but that there is no persuasive evidence in favor of this conception.

The Intrarenal Pelvis.—Ravich[58] reported that a high proportion of patients with essential hypertension have a pelvis situated entirely with the renal parenchyma (intrarenal pelvis) and [illegible]

[illegible] incidence of intrarenal pelvis in hypertensive patients than in normotensive controls.

None of the studies just surveyed shows that essential hypertension results from disease of the kidney or its blood vessels However, they also do not disprove the renal origin of the disease. It is pertinent in this connection that, even though the hypertension produced by the Goldblatt clamp is certainly renal in origin, the actual mechanism of its production is unknown, we do not even know if it is due to elaboration of a pressor body by the kidney or deficiency of an antipressor principle normally formed by the organ, or both In the light of this ignorance of the mechanism of renal hypertension, until either this mechanism or the nature of essential hypertension is unveiled, one can not be sure that the latter is not of renal origin But as yet the available evidence does not indicate even with probability that the origin of essential hypertension lies in the kidney.

CIRCULATING PRESSOR SUBSTANCES IN ESSENTIAL HYPERTENSION

Efforts to elucidate the nature of essential hypertension have naturally included attempts to demonstrate the circulation of a pressor body. Deficiency of a normally circulating antipressor substance also furnishes a conceivable mechanism of hypertension.

Early attempts to demonstrate a pressor body in the blood were concerned with epinephrin, but apart from hypertension due to chromaffin tumors, the search was unsuccessful (page 705). Interest in the Cushing syndrome led to attempts to demonstrate pitressin in the blood and cerebrospinal fluid, but the studies of Page[60] and Hoyle[61] showed that in essential hypertension these fluids contain no excess of pitressin While Henriques and Henriques[404] found the antidiuretic activity of the serum in essential hypertension a little higher than in normals, the differences are not striking.

A number of investigators have thought that they could demonstrate by experiments with strips of artery, perfusion of organs, or injection into animals that the blood of individuals with essential hypertension possesses abnormally strong vasoconstricting properties (for literature, see Leiter[62]). However, careful investigations by Curtis, *et al.*,[63] Wakerlin and Brunner,[64]

. . . ent in only a portion of cases of essential hyper-

w. It is to be remarked, however, that it has by no means been demonstrated and is even improbable that the hypotension of Addison's disease is the result of diminished elaboration of epinephrin; it is more than doubtful that the normal arteriolar tonus is dependent on the epinephrin content of the blood.

. . . and Wiesel[87] thought that they had demonstrated the presence

However, O'Connor[88] and others have shown that this reaction is not specific for epinephrin but is given also by substances formed during the coagulation of the blood Janeway and Park[89] avoided this error by testing the effect of plasma in causing contraction of a strip of surviving artery. With this technique, they were unable to demonstrate the presence of epinephrin in the blood of 6 patients with hypertension. Using a biological test for epinephr

in a dilution of

the venous or arterial blood of . . . hypertension The method was so sensitive that it revealed epinephrin in the blood of the suprarenal vein and as far in the circulation as the right heart, though no further Kobro[91] has developed a quantitative chemical method for determining epinephrin in the blood With this method he found the epinephrin content of the venous blood in essential hypertension in the same range as in normotensives (22 to 79 milligammas per ml).

The failure of such extremely delicate methods to reveal an increase in epinephrin in the blood of hypertensive patients seems fatal to the once promising theory that essential hypertension is produced by an excess of epinephrin in the blood—"the beautiful dream of adrenalinemia," as Janeway[92] called it Smaller quantities of epinephrin than those demonstrable by these methods could have no appreciable pressor effects. Moreover, the demonstration by Beer, King and Prinzmetal[93] of epinephrin in the peripheral blood of a patient with paroxysmal hypertension due to a tumor of the suprarenal medulla shows that present methods suffice to detect epinephrin when this substance circulates in concentration sufficient to produce hypertension (see page 932)

Two other lines of evidence that hyperepinephrinemia is not responsible for the elevation of blood pressure in essential hypertension have been brought out in recent years, especially through the investigations of Goldenberg[94] and his associates:

(a) On intravenous infusion of epinephrin into normotensives at a rate producing elevation of systolic pressure to about 180 mm , Goldenberg and his associates found greatly increased cardiac output, little change in diastolic pressure, sharp drop in peripheral resistance, rise in mean pulmo-

THE ENDOCRINE ORGANS AND ESSENTIAL HYPERTENSION

In recent years, there has been extensive investigation of the relations of abnormalities in the function of the endocrine glands to alterations in blood pressure; and many have thought, with much reason, that at least part of the solution of the riddle of essential hypertension lies in a perversion of the internal secretions.

THE ADRENAL GLANDS

Various theories incriminate both suprarenal medulla and cortex in the pathogenesis of essential hypertension. In the case of the medulla, hypersecretion of epinephrin, and more recently of nor-epinephrin, is the suggested mechanism. With expanding knowledge of the cortical steroids, study of perversion of adrenal cortical function has moved toward the center of the stage in the investigation of essential hypertension.

The Theory of Hyperepinephrinemia.—In view of the fact that the medulla of the suprarenal gland secrets the most powerful pressor substances known, it is a rather obvious thought that hypertension may result from increased function of this organ. Indeed, immediately after the discovery by Oliver and Schaefer[75] of the pressor properties of extracts of the suprarenal medulla, Neusser[76] described two cases of hypertensive disease in young adults, terminating by cerebral hemorrhage, in which "carcinoma" of the suprarenal gland was found but no disease of the kidneys. He believed the hypertension in these cases to be due to secretion of the pressor substance of the suprarenal gland by the tumor. But the actual founder of the theory that hypertension results from increased secretion of epinephrin was Vaquez,[77] who observed a frequent coincidence of suprarenal hyperplasia and hypertension The following lines of evidence have been adduced in the effort to demonstrate that hypertension is the result of increase in the epinephrin content of the blood.

1 Chromaffin tumor of the suprarenal medulla (pheochromocytoma) may produce high blood pressure. The hypertension may be paroxysmal or continuous, the latter closely mimicking classical essential hypertension (*cf.* page 933).

2. Wiesel,[78] Parkinson,[79] and others claimed to have observed hyperplasia of the suprarenal medulla in hypertension On the other hand analyses of suprarenal glands from hypertensive subjects by Elliott[80] and Ingier and Schmorl[81] did not show them to contain more epinephrin than the suprarenals of individuals with normal blood pressure. Mullon[82] noted hyper-

of the musculature of the suprarenal vein in hypertension and in certain cases of renal disease without high blood pressure, the significance of this finding is not clear.

3. Neubauer[84] found that hyperglycemia is a common accompaniment of arterial hypertension In view of the well-known fact that the injection of epinephrin elevates the blood sugar by mobilizing glycogen, this finding has been interpreted in favor of the epinephrin theory of hypertension.

... added another with necropsy proof and a ...

... us, Hoag[99] reported an ... , whose blood pressure was 160/100 mm.; and Bullock and Sequeira[100] a similar case in a child, aged eleven years. Neither had glomerulonephritis nor disease of the urinary passages The final proof that the suprarenal tumor is responsible for the hypertension is afforded by the return of the blood pressure to ... of the growth This was first observed in ...

Since hypertension due to tumor of the adrenal cortex disappears after removal of the growth, it presumably is due to hypersecretion of one or ... t result from ... ion because it ...

2 Vaquez[77] long ago observed that diffuse hyperplasia and circumscribed adenoma formation are common in the adrenal cortex in hypertensive patients Similar observations have since been made by Aubertin and Ambard,[101] Philpot,[102] Oppenheimer and Fishberg,[97] Rhinehart[103] *et al.*, and Russi[104] *et al.* In essential hypertension Rhinehart found almost regularly a grossly thickened and nodular cortex with microscopic hyperplasia of the adrenal cords, which were usually well filled with lipoid droplets, the mean weight of the adrenal in essential hypertension was 4.2 grams more than in their controls. Fisher and Hewer[105] likewise observed increased lipid content of the adrenal cortex in hypertensives. Contrariwise, Dempsey[106] and Commons and Callaway[107] found no correlation between hypertension and hyperplasia and adenoma formation in the adrenal cortex Further investigation is needed to reconcile these important differences In the writer's experience, grossly obvious adenomas are more common in patients with severe hypertension, and the average size of the cortex is greater in the latter Rather[108] found the adrenals enlarged in rats with experimental hypertension

3 Hypertension may be produced in both man and the experimental animal by administration of some of the cortical steroids This was first accomplished with desoxycorticosterone acetate (DOCA) by Loeb[109] and his associates They observed the development of hypertension in patients with Addison's disease as a result of treatment with DOCA Nowadays, most patients with Addison's disease receiving DOCA have hypertension at one time or another; the elevation in pressure develops gradually, is

nary arterial pressure, and most often tachycardia. Each of these findings contrasts with that in essential hypertension. It appears that the pressor effect of epinephrin in man, *in these doses*, contrary to what was long generally thought, is due to increased cardiac output, and that peripheral resistance falls as a result of predominant vasodilatation. This is, of course, diametrically the opposite of the mechanism of elevation of blood pressure in essential hypertension, which is due to widespread peripheral vasoconstriction without change in cardiac output.

(*b*). Piperoxane hydrochloride and other adrenolytic agents depress the blood pressure in hypertension due to pheochromocytoma but not to es-

epinephrinemia.

Nor-Epinephrin.—Nor-epinephrin (arterenol) differs from epinephrin only in the attachment of a methyl group to the nitrogen atom in the latter. Both catechols are present in the normal adrenal medulla and, in widely varying proportions, in pheochromocytoma (Goldenberg *et al.*) It was mentioned above that Goldenberg's studies have shown that, while the hypertension produced by epinephrin is due to increased cardiac output, that of arterenol results from arteriolar constriction.* This brings up the possibility that essential hypertension may be due to increased secretion of nor-epinephrin. However, there is no convincing evidence for this view and much against it; Goldenberg found in humans that piperoxan also depresses hypertension due to arterenol.

Recently, Goldenberg and his associates have suggested that secretion of epinephrin or arterenol may initiate hypertension which is then perpetuated by other mechanisms. They base this theory on observations indicating that continuous hypertension may occur in pheochromocytoma in which there is only intermittent circulation of the adrenergic agent. They found that hypertension persisted in 7 of 12 patients with pheochromocytoma for varying periods, up to 11 months, after the tumor had been resected. Interesting as is the possibility that hypertension may be initiated by adrenergic discharge and then perpetuated by other mechanisms, further evidence is required before it can be regarded as probable.

The Adrenal Cortex.—There is evidence which shows beyond cavil that disease of the suprarenal cortex can produce hypertension and calls for investigation of the possibility that it may be concerned in the pathogenesis of essential hypertension. Some of the evidence for and against this possibility may be outlined seriatim.

1. That disease of the suprarenal cortex can produce hypertension is shown by cases of cortical tumor or hyperplasia accompanied by hypertension. Above were mentioned the two such cases observed by Neusser, another had been published previously by Fraenkel[96] In 1924 Oppenheimer and the writer[97] collected from the literature 13 cases of suprarenal

*

pre
art
of
rate and blood flow.

...one was discontinued. Selye's ... and the observations of Perera[124] on patients indicate the great ... administration of DOCA to nor-...

... of the adrenals. Swingle[125] et al. showed ... sure more readily in the adrenalectomized than in the intact animal. Similarly, Knowlton[126] and her coworkers found in rats with experimental nephritis that cortisone produces far more hypertension in adrenalectomized animals. It is said that potent whole cortical extract, contrary to DOCA, ... hypertension in normal or adrenalectomized ...

... Selye's conception that ... . Hyper-... then be a ...

(c) There is strong evidence that DOCA, and presumably the naturally occurring corticoids which raise blood pressure, produce hypertension at least largely through the intermediacy of alterations in the sodium economy. ... the administration of sodium salts enormously in-...

...ing of DOCA does not elicit hypertension in rats on a sodium-poor diet and tap water, addition of 4 per cent of sodium chloride to the diet pro-... same amount of DOCA. In ... Masugi nephritis, DOCA produced ... intake. Braun-Menéndez finds that when DOCA and sodium salts produce hypertension in rats there are always renal lesions and increase in extracellular fluid volume, and believes that both these factors may be concerned in the causation of the hypertension. However, it seems unlikely that renal lesions play a primary pathogenetic rôle (see below). Much still remains to be learned regarding the nature of the interplay between DOCA and sodium salts in the production of hypertension, but it seems likely that an important factor is the retention of sodium that the hormone produces through favoring ...

... on DOCA hypertension in the Addisonian and normal man, they were unable to correlate the rise in pressure with sodium retention or increase in blood volume.

adrenal disease, Perera[111] *et al.* were able to produce elevation of blood pressure by administration of 10 mg. daily of DOCA plus sodium chloride.

Administration of DOCA to the dog in large doses over a protracted period produces modest hypertension (Kuhlman[112] *et al*). However, this animal is very resistant to the induction of hypertension by DOCA, Visscher[113] did not produce hypertension in dogs by the daily administration for a month of 25 mg. of DOCA and 75 to 125 gm. of sodium chloride. Masson[114] and his associates found that, even after uninephrectomy, DOCA has little effect on the blood pressure of dogs The steroid much more readily causes high blood pressure in the rat (Grollman[115] *et al*, Selye and Hall[116]), which has become the favorite animal for the study of this type of hypertension. Even more susceptible is the chick, in which Selye[117] has found that even small doses of DOCA produce high blood pressure.

Cortisone and ACTH have little effect on the blood pressure in the vast majority of patients with rheumatoid arthritis and other conditions, including the nephrotic syndrome, for which these hormones are used But occasionally, especially with large doses, administration of either of the hormones results in definite rise in blood pressure, which disappears with withdrawal. In Carideo's patient, whom the writer also observed, injection of ACTH for scleroderma was followed by the typical syndrome of malignant hypertension; necropsy revealed renal vascular lesions resembling those of periarteritis nodosa While Perera[118] observed slight decreases in the blood pressure with cortisone, Corcoran[119] *et al* found no significant change in arterial tension in 2 patients with essential hypertension given cortisone for two to five weeks and 2 others given ACTH for the same period.

Selye[120] produced hypertension in rats with injections of 11-desoxocortisone (Reichstein's compound S), but Masson[121] *et al.* were unable to obtain the same result with pellet implants The production of hypertension by desoxocortisone is important because this steroid occurs normally in the adrenal cortex while desoxycorticosterone, though demonstrated by Reichstein in the normal cortex, apparently occurs only in minute quantities.

How DOCA produces hypertension has been the object of much study—largely in the hope of elucidating the rôle of corticoids in hypertensive diseases—but the question has not yet been answered The following are some of the relevant findings:

(*a*) DOCA does not have a directly pressor action like, for example, arterenol, the pressure rises only after
results from changes in the organism
rectly from the circulation of the latter
sensitivity of the vessels to such pressor agents as epinephrin, renin or angiotonin (Masson[114] *et al.*)

(*b*) It is far more difficult to produce hypertension with DOCA in normals than in individuals with Addison's disease. While almost every Addisonian getting therapeutic doses of DOCA has periods of hypertension, large amounts of DOCA must be given for a long time to persons with intact adrenals to produce definite hypertension. When DOCA first became available, the writer administered 15 mg. daily to a patient with far ad-

not by salt alone. These observations on adrenalectomized hypertensive animals and patients contain no evidence that hyperfunction of the adrenal cortex is the *primum movens* in essential or experimental hypertension.

of the latter. Indeed, the experiments of Turner and Grollman[406] indicate that hypertension can be maintained without even the homeostatic participation of adrenal cortical secretion; in totally nephrectomized and adrenalectomized dogs maintained for as long as 40 days by intermittent peritoneal lavage, hypertension equal to that of dogs which were only nephrectomized developed without

5. Victor[140] described hypertensic
and veins at the hilus of one adrenal
result

6 Attempts have been made to obtain information regarding the rôle
of corti-
e—using
enal and
testicular origin—is normal in most patients with essential hypertension (Bruger[142] *et al*). Raab[143] reported that in essential hypertension the resting level of what he regards as adrenocortical compounds in the blood is normal but, contrary to healthy controls, is elevated briefly after exercise. He found no relation between the level of adrenocortical compounds in the

found normal values for formaldehydogenic corticoids in the urine in essential hypertension but

and
ion.
on
of the adrenals in hypertensive diseases It would, however, seem to merit further study

8 The only form of hypertension demonstrably originating in the adrenal cortex, that of the Cushing syndrome, is accompanied by a variety of other manifestations of cortical hyper 3) None of these

nce of 21 hyper-
sugar decreases
, but the rate of
the hypoglycemic state is delayed The normal rate of fall of the blood sugar indicates that there is no increase in circulating anti-insulin agents and, consequently, that the activity of the adrenal cortex or anterior pituitary is not augmented

(*d*) The possibility that DOCA produces hypertension through the intermediacy of the kidney, perhaps by activating the renin-angiotonin mechanism, has repeatedly been considered. Selye[132] showed that in rats, especially if potentiated by unilateral nephrectomy and high sodium intake, administration of DOCA produces arterial and renal lesions. Friedman and Friedman[133] noted that the hypertension caused in rats by DOCA is parallelled by hypertrophy of the kidney. In mice injection of adrenotropic hormone is followed by hypertrophy of the juxta-glomerular apparatus, but there is no evidence of hypertension in the weight of the heart (Dougherty[134]). Zweifach and Shorr[135] detected no indications that DOCA hypertension in rats is due to VEM. Braun-Menéndez showed that when administration of DOCA and sodium salts to rats produces hypertension there are both renal lesions and increase in extracellular fluid volume; he concludes that both the renal lesions and the expansion of the extracellular fluid may be concerned in the genesis of the hypertension. However, it appears that the kidneys are not essential for the pathogenesis of hypertension resulting from DOCA, for Hall and Hall[136] have shown that the blood pressure of rats with such hypertension continues to rise after bilateral nephrectomy; no such degree of hypertension developed in their controls which were nephrectomized without administration of DOCA. The arteriolar and renal lesions which Selye first produced in rats with DOCA and sodium salts may well be the result of the hypertension; they appear similar to or identical with those seen in the contralateral kidney of rats with severe hypertension due to unilateral constriction of the renal artery Such renal lesions may then in turn produce hypertension; they perhaps explain the finding of Friedman and Friedman that when DOCA hypertension has been present for several weeks, it may persist despite cessation of the hormone.

The available evidence would seem to indicate that DOCA produces hypertension through the intermediacy of sodium retention by favoring tubular reabsorption of the cation. According to this view, DOCA hypertension is fundamentally similar to the hypertension produced in rabbits by drinking salt solution (page 724). Whether or not the hypertension resulting from administration of DOCA to a suitably prepared animal or an Addisonian has any relation to human essential hypertension remains to be determined.

4. In his pioneer experiments, Goldblatt[138] showed that, while the elimination of both adrenal medullas does not interfere with the production of hypertension by constriction of the renal artery in dogs, the blood pressure falls to normal after bilateral adrenalectomy. However, the hypertension can be restored by a potent cortical extract, dehydrocorticosterone acetate or DOCA (Page and Lewis[139]) Similarly, relatively small doses of cortisone suffice to maintain blood pressure above normal in patients with essential hypertension who have been treated by total adrenalectomy (page 923). Doses of cortical extract, DOCA or cortisone equal to the amount that maintains hypertension in a Goldblatt dog or adrenalectomized patient will not raise

in a hypertensive

disappeared during hypoadrenalism, but was restored by

... in the cases in which Cushing's syn-

... cortex. However ...

... lobe always have subnormal blood pressure, an observation ... results from his conception that the hypertension of basophilic adenoma results from hyperactivity of the posterior lobe. As a corollary of his theory that the hypertension of the Cushing syndrome results from basophilic hypersecretion, Cushing advanced the hypothesis—for it was no more—that the immediate mechanism of essential hypertension is secretion of an excess of the pressor principle of the posterior lobe. This hypothesis was based largely on his finding that in essential hypertension and eclampsia there is massive basophilic infiltration of the pars nervosa of the hypophysis, though somewhat less in degree than in the syndrome of basophilic adenoma. Cushing also observed an increase in the hyaline substance within the gland, which he considered the secretory product. He called attention to observations by others indicating an increase in the basophiles of the adenohypophysis in renal and other varieties of hypertension. With little supporting evi... ...arded the extent of basophilic infiltration of the neuroh... the cor... hypert... Zimme... ... more common in hypertensives, even these investigators observed many patients with pronounced hypertension but little basophilia and, contrariwise, other individuals with marked basophilic infiltration of the neurohypophysis but normal blood ... study of the pituitary glands fr... 11 with evidences of anteceden... pressure, Spark[159] found no greater degree of basophilic infiltration of the pars nervosa in essential hypertension than in controls of similar age.

Attempts to demonstrate an excess of pitressin in the cerebrospinal fluid or blood of patients with essential hypertension or with the Cushing ...

... tension or the Cushing syndrome.

The possibility that excessive secretion of ACTH participates in essentia... hypertension merits consideration. In rare cases—the writer has see... two—administration of ACTH to normotensives leads to malignant hyper... tension. Appel *et al*[161] observed hypertension in 3 of 17 normotensiv... soldiers to whom they gave a daily intravenous injection of 20 mg. ... ACTH for thirty-one consecutive days. However, there is no good eviden... that hypersecretion of ACTH is primarily concerned in the pathogenes... of essential hypertension (*cf.* also Selye's stress theory, page 741). Sin... ACTH stimulates secretion of multiple, if not all, the hormones of t...

10. By studying the sodium and chloride concentrations in the sweat, Davies and Clark[149] found evidence of hyperactivity of the salt-retaining hormone of the adrenal cortex isnot more than 20 per cent of cases of essential hypertension; these perhaps correspond to the patients with essential hypertension in whom Schroeder[150] and these investigators pointed out the existence of a syndrome—including hypertension, obesity and menstrual irregularities—simulating adrenal cortical hyperfunction. However, Davies and Clarke's observations on the sweat revealed no evidences of adrenal cortical hyperfunction in the large majority of hypertensives. The observations of Eisenberg *et al.*[151] on the sodium concentration in the sweat also revealed no evidence of increase in the level of "electrolyte-influencing" adrenal cortical steroids.

Summary.—That adrenal cortical activity can produce hypertension is proved by the Cushing syndrome. Also demonstrated is that neither clinical nor experimental renal hypertension is maintained in the absence of the adrenal cortex or replacement therapy. But *there is no convincing evidence that essential hypertension originates in the adrenal cortex or that the latter plays other than a secondary and homeostatic rôle in the disease*

THE HYPOPHYSIS

The classical disturbance of pituitary secretion, acromegaly, presents no characteristic abnormality in blood pressure. Nevertheless, in view of the long known pressor property of extracts of the posterior lobe, it is not surprising that the possibility that the hypophysis might be concerned in the genesis of high blood pressure has been discussed repeatedly. Some of the earlier observations were mentioned in the first two editions of this book, but none of them carried any conviction, and it was not until the description of the Cushing syndrome that the pituitary factor in hypertension was seriously studied.

That hypertension can exist in the absence of pituitary activity has been shown experimentally. In Goldblatt dogs, Page and Sweet[152] found that while hypophysectomy produces a fall in pressure, tighter constriction of the renal arteries causes the pressure to rise further. Goldblatt[153] *et al* showed that complete hypophysectomy does not prevent the development of hypertension when the renal arteries are constricted in the dog or permanently lower the pressure in such a dog. Anderson[154] and his associates showed that when the blood pressure falls following hypophysectomy in rats with renal hypertension, the elevation is restored by ACTH. Braun-Menéndez[155] long ago found that hypophysectomy produces a fall in blood pressure in normal dogs, since he showed that removal of the posterior lobe does not affect the blood pressure, the fall is due to loss of adenohypophyseal function, perhaps the result of elimination of stimulation of the adrenal cortex by ACTH.

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C........g

is a cardinal feature of this syndrome. The data now available indicate that the hypertension of the Cushing syndrome is a manifestation of hyper-

of menopausal hypertension probably

only when the woman comes to the

with the hypertension; the results of

symptor

treatmei

As yet,

the pathogenesis of essential hypertension.

Heart. Another group of cases of essential hypertension which

organs. Cardiac disturbances were described in patients with

1895. Of 951 cases of uterine fibroid collected from the

found in association with fibromyoma. It would seem, however,

myoma heart is not a unitary concept In some instances, the enlargement of the heart with such subjective disturbances as dyspnea and palpitation is the result of the anemia produced by long-continued uterine bleeding Not rarely, associated obesity produces dyspnea and other symptoms In other cases, however, there is arterial hypertension which may cause cardiac symptoms. The nature of the relation between fibroids and arterial hypertension, if any, is not clear. Polak *et al.*[170] found that fibroids have no effect on the blood pressure in young women, when hypertension was associated with fibroids in their cases, it was always in older women Mueller[171] believed that fibromyoma not uncommonly results in arterial hypertension He stated that he had seen several cases of fibromyoma with hypertension in which operative removal of the tumor

age groups In an exact statistical investigation, Alvarez and Zimmermann[173] found that women with fibroid disease have higher average blood pressures than normal women In fact, they found that various abnormalities of the female reproductive organs—masculine distribution of body hair, sexual anesthesia, fibroids of the uterus, and pelvic conditions requiring ovariectomy or hysterectomy—are associated with high average pressure Alvarez and Zimmermann believe that in these cases elevation of blood pressure occurs only in those with an inherited tendency to hyper-

adrenal cortex, the absence of other manifestations of the Cushing syndrome militates against the existence of ACTH excess in essential hypertension.

That the insulin tolerance of hypertensive patients affords no indication of increased activity of the anterior pituitary was mentioned on page 711.

In pursuance of his extensive experiments on hypothalamic function, Heinbecker[162] has evolved a hypothesis of the pathogenesis of essential hypertension involving a pituitary imbalance. He believes that nervous influences from the frontal lobes depress the supraoptic and paraventricular nuclei of the hypothalamus. This depression causes decreased neurohypophyseal secretion, in consequence of which the eosinophiles of the adenohypohpysis are stimulated to increase their output of ACTH. More evidence is needed before these conceptions can be regarded as other than hypothetical in their relation to essential hypertension.

In brief, *there does not appear to be evidence that the pituitary plays other than a homeostatic rôle in the pathogenesis of essential hypertension.*

THE GONADS

Menopausal Hypertension.—The widely accepted concept of menopausal hypertension originated with Huchard,[163] who observed that hypertension often appears at the time of the menopause; he spoke of "hypertension artérielle de la ménopause." Such hypertension may accompany or follow either the natural menopause or that produced by either operative or roentgen castration However, well-marked hypertension occurs in only a comparatively small proportion of women at or soon after the menopause; Lehfeldt[164] noted it in only 16 of 111 women passing through either a natural or an artificial menopause, and in several of these it may have been due to other causes. He found that abnormally great fluctuations in blood pressure are a more frequent climacteric manifestation than is true hypertension; such fluctuations exceeding 15 mm. in the systolic pressure were present in 23 per cent of climacteric women In 200 women desiring relief of menopausal symptoms, 179 of whom had been surgically castrated, Taylor[165] *et al.* found no greater incidence of hypertension than in the general population, only 6 developed high blood pressure following the menopause and 5 of these were over forty years of age

It would thus appear that in a strict sense *there is no such entity as menopausal hypertension*; the incidence of hypertension at or shortly after the natural or induced menopause is hardly greater than in women of the same age without ovarian failure. It is true that on rare occasions one encounters an abrupt rise in blood pressure in the months following surgical or roentgen castration, but a similar rise is sometimes seen in other women and in males. The usually modest fluctuations in blood pressure that may accompany the vasomotor phenomena of the climacteric are by no means always indicative of future hypertension. Another evidence that hypertension in climacteric women is not due to elimination of ovarian activity is the failure of estrogens to lower the blood pressure. Ayman[166] and Mayer[167] and his associates saw little effect on hypertension from the administration of estrogen; my experience has been the same even when the vasomotor phenomena and other symptoms of the menopause are

blood volume. In favor of such a conce... ...ally patients with both thyrotoxicosis and

tion of the elevated ... ...ity of the cases

A previously healthy boy, aged sixteen years, rather suddenly started to gain weight, until his obesity became extreme. Development of the primary and secondary sexual characteristics was greatly retarded. His blood pressure rose to 175/135 mm He died of cerebral hemorrhage at the age of twenty-one years. At necropsy, very extensive atrophy of the thyroid gland was found. The pituitary and suprarenal glands presented no struct... ...the testes showed only diminished spermatogenesis

changes t...

I have also seen another instance of marked hypertension in a myxedematous woman, aged thirty-two years, though it was but little lowered when she took large doses of thyroid which relieved her other symptoms. Moreover, a survey of the reported necropsies in myxedema (see the paper just cited) reveals that cardiac hypertrophy, granular kidneys, and severe

blood pressure in some patients with essential hypertension I have seen no evidence of this While there is often some reduction in blood pressure when obese individuals with hypertension take thyroid extract in the belief that it helps in weight reduction, the lowering in pressure is

The Liver and Pancreas.—The functions of the liver and the pancreas in hypertension are discussed below, there is no evidence that either is concerned in the pathogenesis of the disease.

Summary.—That hormonal disturbances, *per se*, can produce chronic hypertension having the characteristics of essential hypertension is shown by the primary or secondary hyperfunction of the adrenal cortex that re-

or adequate replacement therapy is necessary for the maintenance of any form of hypertension. Nevertheless, *there is as yet no proof that essential hypertension results from an endocrine disturbance.*

of similar age. Since the hypertension occurred more often in women in whom the intravenous pyelogram disclosed dilatation of the ureters, they believe that interference with urinary flow over long periods may be concerned in the genesis of the elevation in pressure.

The Testis.—There is no indication that the testis is concerned in the pathogenesis of essential hypertension. While Steinach,[177] Walker[178] and others reported that testosterone propionate may lower the blood pressure of hypertensives, this was not confirmed by Green[179] and Lattimer.[180] I have not noted any effect of testosterone on elevated arterial pressure in men being treated for the "male climacteric." With the Hamilton manometer, Blackman[181] and his associates found no change in the arterial pressure of puppies from testosterone. Adams[182] observed hypertension in a man of twenty-two years with a chorionepithelioma of the testis whose urine contained large amounts of gonadotropic hormone and cites other malignant testicular tumors with positive Friedman tests in which there was hypertension. Hypertension in such testicular tumors may be related to the high blood pressure of the toxemia of pregnancy or the Cushing syndrome, but throws no light on the pathogenesis of essential hypertension

There would seem to be no evidence that the gonads are concerned in the causation of essential hypertension. Nor does gonadectomy in either sex have any effect on experimental renal hypertension in the dog (Goldblatt).[153]

THE THYROID

Most patients with essential hypertension have no abnormality in oxygen consumption (*cf.*, however, page 818) Thyroidectomy does not interfere with experimental renal hypertension (Goldblatt).[153] Nor do clinical observations, as will be seen in the following, afford any evidence that the thyroid is concerned in the pathogenesis of essential hypertension.

Hyperthyroidism.—The large majority of individuals with Graves' disease, particularly the younger ones, do not have true hypertension. As is clearly seen from the tables of Plummer,[184] the systolic pressure in thyrotoxicosis is usually moderately or even considerably elevated, but the diastolic pressure is normal or more often somewhat low. Apart from these expressions of the alterations in circulatory dynamics due to hyperthyroidism, there is a group of cases in middle life, studied especially by Boas and Shapiro,[185] who have both true diastolic hypertension and thyrotoxicosis It is not uncommon for patients with long-standing thyrotoxicosis but no diastolic hypertension at first to develop diastolic hypertension when he, or more often she, reaches middle life. Hurxthal[186] found no evidence that hyperthyroidism leads to essential hypertension, but I have a decided impression that essential hypertension is more common in middle-aged individuals who suffer, or previously suffered from Graves' disease than in the general population (see also p 819). Parkinson and Hoyle[187] have also observed the frequent concomitance of hypertension and hyperthyroidism in individuals over the age of forty years However, the hypertension in such individuals cannot be attributed directly to the thyrotoxicosis for much more severe Graves' disease in the young, even though present for years does not produce elevation of the diastolic pressure It seems likely,

the regular meals,

tive material ingested by
though they do not take
which, however, has scarce
drunk beer in quantities comparable to those ...
taken in Munich. On restriction of the diet, particularly in obese persons, it is not uncommon to see a moderate drop in blood pressure.

On the other hand, there are many persons who have partaken of a seem-... throughout a long life and have normal blood

... inference from the effects of spontaneous and ... the ap-... essential

... tinguished

There is a widespread popular belief, also held by such ... physicians of a former generation as Huchard and, with reservations, Allbutt, that excessive ingestion of meat is particularly potent in elevating the blood pressure However, there seems to be little or no evidence for this opinion. It will be pointed out below that the evidence that a high-

known as essential hypertension regarded it as the result of primary disease of the kidney, the hypertension being a consequence of the retention of pressor substances These pressor substances were generally thought to be end-products of protein metabolism This theory is, however, rendered unten-

the tubules, but there were also glomerular and interstitial changes Similar results were obtained by Pelvogt, *et al* [193] Evans and Risley,[194] Nuzum, *et al* [195] and Blatherwick and Medlar.[196] In the experiments of the last named investigators and others, the animals developed renal insufficiency with nitrogen retention Moise and Smith[197] and Jackson and Moore[198] found that after the removal of one kidney in the rat, a protracted high-

the administration of nephrotoxic serum, a very high protein diet prevents healing Newburgh and his associates were also able to produce renal

METABOLIC FACTORS IN THE ETIOLOGY OF ESSENTIAL HYPERTENSION

In recent years, metabolism in essential hypertension has been studied extensively, and there have been advanced various theories of essential hypertension as a metabolic disease. Though critical consideration shows that the results of these investigations have been essentially negative insofar as clearing up the nature of essential hypertension is concerned, they have nevertheless served to elicit many facts of theoretical and practical significance.

Food Intake.—Both the laity and some of the profession have long thought that there is a correlation between quantity of food ingested and the blood pressure. This belief is not entirely without foundation. The very exact experiments of Keys and his associates[191] have shown that protracted semistarvation leads to fall in blood pressure in healthy young men. On a daily intake of 1,600 calories with 49 Gm. of protein for six months, at the end of the period their subjects showed a fall in blood pressure from the control level of 106.5/69 9 mm. to 94.7/64.5 mm.; the diminution in blood pressure accompanied a decrease in heart rate to 37 beats per minute and in basal metabolism to minus 39.9 per cent The blood pressure quickly mounted during rehabilitation from the semistarvation, and even rose above the control levels when the subjects ate excessively. Brozek *et al.*[191] cite some very interesting observations during World War II, showing that protracted undernutrition results in decrease in blood pressure in both those with previously normal pressure and hypertensives. Especially noteworthy and detailed were the observations during the siege of Leningrad Accompanying the emaciation of the semistarvation during the siege were a decrease in blood pressure in normotensives, a diminution in the number of hospital admissions for hypertension, and reduction to normal or near normal of the blood pressure in many chronic hypertensives. They cite similar observations by Lups and Francke in Holland in the winter of 1944–45, when the blood pressure fell in 74 per cent of normals and 93 per cent of hypertensives who lost weight Even more interesting was the remarkable increase in the incidence and severity of hypertension in Leningrad after the siege was lifted and food consumption rose. Compared to the prewar incidence of hypertension, there was a fourfold increase between twenty and thirty-nine years of age, twofold between forty and forty-nine, and threefold over fifty years. Moreover, the frequency with which hypertension entered the malignant phase rose above the prewar percentage during this period of renewed availability of food after protracted semistarvation

Gluttony ha [illegible] nsion, a view which has bee [illegible] Stengel,[267] and many others. [illegible] contingent of those with essential hypertension have been gluttons for many years I have repeatedly been struck by the unusual appetites of relatively young individuals with essential hypertension, particularly before symptoms appear. It should be borne in mind that many who claim to be temperate in food actually eat a great deal. This is especially true in the case of

the blood pressure of 39 patients with long-standing essential hypertension did not change.

Studies on dogs with experimental renal hypertension do not indicate that a high *protein* diet aggravates the high blood pressure. While early observations by Verney and Vogt,[211] Cash and Wood,[212] and Maclachlan and Taylor[213] seemed to suggest that *feeding* large amounts of meat to Goldblatt dogs augmented the hypertension, this has not been borne out by later studies by Phillipsborn *et al.*,[214] Goldblatt *et al.*,[215] and Page and Lewis.[216]

In brief it may be stated that no convincing evidence has as yet been pr ... ing in essential hyper-
te ... 266) that

in health blood pressure tends to rise with increasing weight. In accord with this, obesity is an exceedingly frequent concomitant of essential hypertensio
clinic of the
associates f
times more
obese wom
the lean
et al reve
in the overweight ...
quent in hypertensive men as in the general population, but in women the difference was very slight. They noted, however, that body weight more than 25 per cent above the standard is hardly more frequent in hypertensives than in normotensives. I have likewise noted that *extremely* obese individuals do not have a notably great incidence of hypertension, especially if one allows for overestimation of the blood pressure because of a very obese arm, and that when it occurs the hypertension rarely enters the malignant phase. Reduction of weight by dietary restriction in obese individuals with hypertension is occasionally accompanied by considerable fall in blood pressure, which usually rises again if the patient gains weight. By no means all patients with essential hypertension are obese, some are very spare. And many individuals with essential hypertension lose a great deal of weight as the disease progresses, despite the fact that the blood pressure is rising. This is especially true if they enter the malignant phase of the disease.

It appears evident that obesity in itself does not cause hypertension, for extremely obese individuals may have low blood pressure, even though there is no evidence of cardiac weakness. Obesity, like hypertension, is often an inherited characteristic, and it seems probable that the same constitutional type is predisposed to both obesity and hypertension, which tend to appear at the same period of life. Likewise, overeating tends to

tion that obesity causes hypertension, for dietary *restriction* may have a similar effect on the blood pressure of thin persons.

lesions by the intravenous injection of certain amino-acids, which they therefore consider as responsible for the renal damage. Squier and Newburgh[199] claimed that forced protein feeding results in the appearance of red blood corpuscles in the urine of health ... Newburgh *et al.*[200] found ...

... different high-protein diets may injure the kidneys They followed the blood pressure of rabbits kept on a high-protein ration for a protracted period and found that hypertension was produced.

On the other hand, Drummond *et al.*[201] Jackson and Riggs,[202] Anderson,[203] and Osborne[204] *et al.*, did not find any notable lesions of the kidney, apart from ... protein diet. It is, ... amount of protein in the diet was solely responsible for the lesions of the kidneys in the experiments in which they were produced

Moreover, the significance of the experiments with high-protein feeding for hypertensive disease in man is far from clear. As far as glomerulonephritis is concerned, there can be no doubt that ...

... produced, they bore no resemblance to the arteriolosclerotic renal lesions found in essential hypertension. Nor does clinical experience lend any support to the theory that essential hypertension results from excessive protein intake. Mosenthal[205] and Strouse and Kelman[206] found that the ingestion of a high-protein diet over a considerable period by patients with hypertension does not elevate the blood pressure, and neither does a low-protein diet lower it That a high-protein regimen does not *per se* produce hypertension is well shown by Lieb's[207] report on Stefannson, the Arctic explorer. He spent eleven and a half years within the Arctic Circle, during which he lived on an exclusive meat diet for a number of days, totalling nine years, subsisting nine successive months on meat alone Despite this, his blood pressure was 115/55 mm Thomas[208] found that the Eskimos, whose diet is practically entirely carnivorous, show no increased incidence of hypertension On the other hand, Faber[209] observed an individual who had been a vegetarian for twelve years, but nevertheless had a systolic blood pressure of 220 mm. I have seen several vegetarians with essential hypertension

Evidence against the view that a high protein intake is concerned in the pathogenesis of essential hypertension is afforded by the results of low protein diets in the disease It is true that the blood pressure of some patients falls on the Kempner rice diet (20 grams of protein daily), but in others the blood pressure remains high despite protracted conscientious adherence to the diet to the point where malnutrition develops, and when lowering of pressure occurs it may be reversed by salt ingestion with no increase in protein intake. Kohári-Kuchárik[210] observed that during the siege of Budapest, when animal proteins were unobtainable for ten months,

very high diastolic pressure, notably those with the clinical picture of the n ... cholesterol is definitely elevated, to between 3 ...

analysis of the serum lipoproteins by Gofman's technique

Carbohydrate Metabolism.—It was mentioned above that hyperglycemia and diminished sugar tolerance are not uncommon in essential hypertension. In 23 of 32 hypertensive patients Harris[226] found diminished glucose tolerance in that the peak of the curve exceeded 170 mg. per cent or the glucose level did not return to normal within two hours. Statistics of the incidence of hypertension in manifest diabetes have not been wholly

a blood pressure above 150/90 mm. Joslin found that ... per cent ... diabetics between twenty-one and fifty years and 33 per cent of those over fifty years of age have systolic blood pressures over 150 mm. Kramer[232] observed hypertension in 39 per cent of 500 diabetics. Major[233] found the systolic blood pre... mal controls. In ... is a great rarity, ... entirely to its occurrence in diabetics over forty years of age. The average systolic blood pressure of Joslin's diabetic patients below the age of forty years was almost exactly equal to the average for healthy individuals, but the diabetics over forty years had blood pressures averaging 10 mm., and those above fifty years, 20 mm. above the normal. Bell's[234] autopsy statistics show that hypertension is much more common in elderly diabetics

p. 811, remains to be determined.

There does not seem to be evidence that diabetes *per se* plays any rôle in the production of essential hypertension. The fact that hypertension is

Cholesterol Metabolism.—Disturbances in cholesterol metabolism have also been thought to play a part in the causation of essential hypertension Schmidtmann[220] was able to produce hypertension in rabbits by feeding them cholesterol over a long period. But later the blood pressure fell despite the continuation of the cholesterol feeding and the persistence of hypercholesteremia. She believes that the cholesterol as such does not elevate the blood pressure but serves to sensitize the vessels to pressor substances. Thomas[221] found that while a single injection of cholesterol does not raise the blood pressure, repeated injections cause prolonged hypertension. These results were contradicted by Thoelldte,[222] who was unable to produce hypertension in rabbits by cholesterol feeding over as long a period as four hundred and twenty-three days, though marked arteriosclerosis resulted. Recently, Hoffman[223] and his associates observed the development of definite hypertension in 5 of 12 rabbits fed 3 to 20 grams of cholesterol weekly for twelve to one hundred and four weeks. Of the 5 rabbits with hypertension, 4 had amyloidosis or paramyloidosis at necropsy; this lesion was not present in the other animal, which maintained a mean arterial pressure of between 140 and 205 mm. Hg (direct measurement) for thirty weeks. These observations raise the possibility that when hypertension is produced in rabbits by cholesterol feeding, a renal lesion may be concerned in the pathogenesis

Some investigators have found that the cholesterol content of the serum is commonly increased in essential hypertension. Westphal[224] observed hypercholesteremia in 71 per cent of his cases of essential hypertension, and advanced on tenuous grounds the hypothesis that increased cholesterol content of the plasma sensitizes the arterioles to pressor substances. Wacker and Fahrig[225] also found increased cholesterol content of the blood in 75 per cent of their hypertensive patients; phospholipids and triglycerides were similarly elevated. They found that the proportionate increase of the different lipid fractions in essential hypertension corresponds closely to what they observed during physical exercise in normal controls. For this reason, they ascribed the elevation in blood lipids in essential hypertension to increased demand for these substances by the hypertrophied heart and the hypertonic arterioles Wacker and Fahrig's assumption was that the fatty bodies are mobilized into the blood from the depots in higher concentration as is true of sugar during exercise Harris[226] also found that total lipids, cholesterol, fatty acids and phosphatides are significantly increased in the serum in essential hypertension; the average serum cholesterol of 125 normotensives was 177 mg per cent and of 152 hypertensives 237 mg per cent

Contrariwise, Page[227] and his associates found that the concentration of cholesterol and the other lipid fractions in the serum is normal in uncomplicated essential hypertension. Only in the malignant phase did they find high lipid values. Likewise, Hatch and Kendall[228] found the serum lipid patterns (free and esterified cholesterol, phospholipids and triglycerides) normal in patients with severe hypertension on a normal lipid intake. My experience has also been that the serum lipids are within normal limits in the large majority of patients with essential hypertension, though the average is higher than in normotensives. However, in occasional patients with

I ... varieties of experiment, Selye[84] has shown that sodium salts ... and renal lesions produced by ... ere is much in favor of the view ... with the intermediacy of sodium

sult of salt and water retention.

The above findings are suggestive that sodium retention favors rise in blood pressure. But there does not appear to be evidence that sodium retention is primarily concerned in the pathogenesis of human essential hypertension and much that speaks against it:

1 In most of the clinical observations on the effects of salt restriction in ... the salt intake was not the only variable factor

in blood pressure on salt restriction and the rise on salt supplementation was small

2 In the vast majority of patients with uncomplicated essential hyper- ... and chloride contents of the plasma are normal.

large material that has become available since the introduction of flame photometry Hypertensive patients without cardiac or renal failure excrete salt loads in at least normal fashion In fact, Green *et al.*[246] found

had previously found that tubular reabsorption of chloride is reduced in hypertensives

3 In hypertensive patients in whom heart failure is treated by salt ... ften observes maintenance of ... chloride levels in the plasma. ... ure of more than 210/120 mm. despite plasma sodium of 115 mEq and chloride of 80 mEq per liter as contrasted with normal levels for these ions prior to the inauguration of dehydration Likewise, *in uremic vomiting high blood pressure* may persist despite marked fall in plasma sodium and chloride. Such cases are ... ere is no paral- ... blood pressure, ... nothing of the electrolyte concentrations in the cells, they do show that there is no relation between the level of the blood pressure and the sodium and chloride content of the extracellular fluid

rare in young diabetics, even though they have had the disease in extremely severe form for years, shows that diabetes does not cause hypertension. This was well illustrated by Mosenthal in a lecture in which he showed charts of diabetics who had had marked hyperglycemia for many years without any elevation of blood pressure. In fact, strikingly low blood pressure is fairly common in diabetics who have been undernourished for a protracted period. The reduction in blood pressure that occasionally follows successful treatment of complicating diabetes does not indicate the diabetic origin of the hypertension, for such treatment usually includes limitation of diet and often reduction in weight, factors which may lower the blood pressure in non-diabetic individuals.

In some of th [illegible]

However, it seems probable that the hereditary predisposition which plays so large a part in both essential hypertension and diabetes is not uncommonly present in the same individual. Essential hypertension, diabetes mellitus, and obesity are a triad which is often found in the same person, and it is not uncommon to find one or more of the three in several members of the same family. This fact points strongly to a constitutional peculiarity being responsible for both the diabetes and the hypertension

The lack of evidence for the hypothesis that both hypertension and hyperglycemia are the common result of an excess of epinephrin in the blood was pointed out above.

Salt Metabolism.—The theory that hypertension results from the retention of sodium chloride in the organism was advanced by Ambard and Beaujard,[235] who observed that the blood pressure of hypertensive individuals is elevated by the ingestion of salt and lowered by the elimination of salt from the diet In more recent years, Allen and Sherrill and others (see Chapter 28) have succeeded in lowering the blood pressure notably in many patients with hypertension by a salt-poor diet. Perera and Blood[236] found that the hypertensive patient is more resistant than the normal to the dehydrating effect of salt restriction Also consistent with the theory that abnormalities in the salt economy may be concerned in the pathogenesis of hypertension are the association of salt deficiency with hypotension in Addison's disease and the elevation in blood pressure produced by the administration of salt to such patients In view of the fundamental rôle of the adrenal cortex in the regulation of sodium exchange, the possibility immediately presents itself that any part that sodium may play in the pathogenesis of hypertension may be through the intermediacy or as a result of alterations in cortical function

Experimentally, Sapirstein[237] and his associates have produced hypertension in rats by substituting hypertonic sodium chloride solution for their drinking water; the rise in blood pressure appeared after they had been drinking the saline for one to four weeks The same was previously accomplished in the chicken by Lenel[238] *et al* Grollman and Harrison[239] showed that rigid salt restriction lowers the blood pressure of hypertensive rats Landis and Abrams[240] found that rats with renal hypertension avoid sodium solutions when given their choice of various solutions for drinking.

han incidentally associated," note
igh arterial pressure. He quotes
nore tense in irregular than in regular gout. Gemmel,[258] based on an
that the blood pressure is elevated in

a severe paroxysm as a result of the pain,
appears in the gouty, if at all, during middle and late life. Gout may be present in a severe form for many years with normal or even low blood pr

plication in gout has been known since Garrod's classical found urate deposits in the kidneys of all his patients with tophaceous gout and many of the others. Most patients with long-standing gout have proteinuria. renal excretory function develop in a high propor-

than 45 cc Eighteen of their 22 patients had regard as the earliest evidence of impairment of renal function in gout. The depressed renal function may lead to uremia, which is the cause of death in a significant proportion of the gouty. At necropsy, almost all gouty patients show renal lesions. The classical gouty change in the kidney apparently starts with precipitation of urates in the collecting tubules. This is followed by necrosis of the epithelium, interstitial inflammatory reaction and fibrosis. In 2 of Mallory and Brown's[262] 6 cases there was marked pyelonephritis (multiple abscesses in 1) and in another healed pyelonephritis. Their findings indicate that the pyelonephritis developed in tubules obstructed by urates, the same was true in a case reported by Spitz *et al.*[263] and in one seen by the writer. As in all forms of chronic pyelonephritis, obstructive lesions of the renal arterioles may develop. calculi and as- kidney its with extensive kidney damage of uratic origin, it appears entirely logical to regard hypertension as renal in origin.

sential hypertension

THE LIVER AND ESSENTIAL HYPERTENSION

It has long been known that injection of extracts of various organs has a depressor effect. Macdonald[268] and Major[269] observed that liver extracts produce a particularly striking depression of blood pressure in many cases of essential hypertension, but Major found little effect on the normal blood

DOCA than without this hormone. *Soffer*[247] *et al.* showed that this is the normal response, in contrast to the "diuresis" of salt that follows administration of DOCA in the adrenal cortical hyperfunction of Cushing's syndrome.

6. Any theory that would attribute essential hypertension to *renal retention* of sodium or chloride meets the objection that in the Goldblatt dog, which certainly has a renal hypertension, the sodium and chloride clearances are normal *(page 320)*. And in man with uncomplicated essential hypertension, Brodsky and Graubarth[403] found that, under hydropenic conditions, renal conservation of sodium chloride may be defective, the loss of sodium chloride in the urine exceeding the normal.

The evidence available at present thus does not indicate a primary rôle of derangement in sodium or chloride metabolism in essential hypertension.

There have been a few studies of other electrolytes in essential hypertension, but they have shed no light on the pathogenesis of the disease:

Potassium.—In an extensive series of investigations, Kylin[250] found the potassium content of the serum slightly elevated and the calcium content diminished in essential hypertension. However, it seems probable that these findings were due to defects in method; in uncomplicated essential hypertension both the potassium and calcium levels in the serum are within normal limits. The decrease in blood pressure that De Wesselow and Thomson[254] observed in hypertensive patients given potassium salts was hardly of significant degree. Recently, Friedman[399] and his associates have observed that a diet deficient in potassium lowers the blood pressure of normal and hypertensive rats and decreases their peripheral vascular reactivity Correspondingly, Perera[400] has found that a low potassium diet produced a small but what he regards as statistically significant fall in resting blood pressure in 6 series of observations in 4 patients with essential hypertension. More observations along these lines are needed before they can be interpreted.

Calcium.—Freeman and Farmer[251] stated that the percentage of serum calcium present in diffusible form is somewhat lowered in essential hypertension, but I am not aware that this has been confirmed Harris[252] claims that protracted administration of calcium to rabbits produces hypertension; this also requires verification. In patients, Kesson and McCutcheon[253] found no evidence that protracted retention of calcium raises the blood pressure

Magnesium.—Weil[256] and Wacker and Fahrig[225] found that the magnesium content of the blood averages slightly above normal in hypertension, but the differences do not seem significant and have not been verified.

Thiocyanate.—Wacker and Fahrig[225] detected no abnormality in the thiocyanate concentration of the blood in hypertension.

Bicarbonate, phosphate and *sulfate* are within normal limits in uncomplicated essential hypertension

As yet, no abnormalities in the electrolytes of extracellular fluid have been correlated with hypertension.

Purine Metabolism.—Hypertension is frequently present in gouty subjects. The first systematic student of hypertension as such, Allbutt,[257] though he believed that "regular gout and high pressure are not more

Apart from the transitory hypertension which follows emotion, neurogenic hypertension occurs in some diseases of the central nervous system ... section of the moderator nerves.

Mediation of Neurogenic Hypertension ... believe that neurogenic hypertension is principally or totally mediated through the vasomotor nerves. In accord with this general held conception is the finding that experimental forms of neurogenic hypertension are abolished by sympathectomy (see below). In recent years, however, experimental evidence has been adduced indicating the possibility of renal and humoral mediations of neurogenic hypertension.

Renal Mediation of Neurogenic Hypertension —There are forms of experimental renal hypertension which are effectuated through the kidney. ... the kidney produces ... presumably chemical ... Kottke[279] *et al.* by ... But even after the hypertension thus produced had been maintained by stimulation for as ...

except for sparing the nerves to the kidneys. Hoff[280] and his associates showed that when hypertension is produced in the cat by electrical stimulation of certain areas of the frontal cortex, the volume of the kidneys de... They showed by ... ische... blood of 3 of their 5 stimulated animals. Suggestive as are these experiments, it remains to be demonstrated that renal vasoconstriction and the consequent functioning of a renal pressor mechanism play any part in clinical neurogenic hypertension.

Humoral Mediation of Neurogenic Hypertension —Recently, Taylor, Page and Corcoran[281] have adduced experimental evidence that the brain can secrete a pressor substance into the blood stream. They named the substance *cerebrotonin*. By ingenious cross-circulation experiments, they have shown that centripetal stimulation of the cut vagus in the neck results in liberation into the circulation from the dog's isolated head of a vasopressor substance, which their evidence indicates is secreted by the brain. Binet and Burstein[282] also showed that centripetal vagal stimulation in the dog induces liberation into the blood stream of a vasoconstrictor substance. The vasopressor action of this cerebral secretion is not inhibited by adrenolytic agents, which shows that it is not epinephrine or arterenol. Taylor *et al.* find that the cerebral vasopressor substance is strongly inhibited by 1-hydrazinophthalazine and does not induce tachyphylaxis, these properties, they believe, differentiate it from pitressin, which Binet and Bur-

pressure. These observations in essential hypertension have not been confirmed (4th ed., page 712). There is no convincing evidence that such depressor effects as liver extracts may have are different from those of a wide variety of organ extracts. James *et al.*[270] claimed that the method of preparation of the liver extracts used by Macdonald and Major precluded their containing histamine, choline or peptones, the "nonspecific" depressor substances present in many organ extracts. Contrariwise, Burnett[271] believes the depressor substance in liver extract is histamine.

Ferritin, the depressor component of Shorr's vasoregulatory system (page 331), and hypertensinogen (page 324) are formed in the liver. However, there is no evidence that any form of hypertension results from excess of the former or deficit of the latter Haynes and Dexter[272] found the hypertensinogen content of the blood normal in hypertension without renal insufficiency

Raaschou[273] found that the incidence of hypertension in 102 women with subchronic hepatitis studied at necropsy was [illegible] that the hypertensinogen content of the blood is decreased in some patients with hepatic insufficiency is not demonstrated Nor is the interpretation clear of Raaschou and Trautner's[402] finding that obstruction of the common bile duct lowers the blood pressure of dogs with experimental renal hypertension.

As yet, there is no substantial evidence that any abnormality of liver function exists in essential hypertension.

THE NERVOUS SYSTEM AND ESSENTIAL HYPERTENSION

In view of the usual pressor response to disturbing emotion, it is not surprising that a nervous pathogenesis has been considered from the earliest studies of what is now known as essential hypertension.* Such a line of thought is rendered all the more appealing by the unequivocal evidence that increased peripheral resistance is the immediate mechanism of the rise in blood pressure, for the vasomotor nerves play a great part in the regulation of the peripheral resistance, especially in determining the partition of blood between different organs. Nevertheless, when it was found that denervation of the kidneys and sympathectomy do not interfere with Goldblatt hypertension (page 321), many deprecated the significance of nervous factors in clinical hypertension But the studies of the past few years have indicated the need for reappraisal of the rôle of the nervous system in essential hypertension. And in accord with the *Zeitgeist* an increasing body of critical opinion, not confined to those of primarily psychiatric orientation, regards essential hypertension as a psychosomatic disease,

* Peculiarly enough, Rokitansky,[274] the morphological pathologist *par excellence*, attributed "idiopathic cardiac hypertrophy," doubtless predominantly our essential hypertension, to a disturbance of innervation Laycock,[275] another early student, suggested that Bright's disease results from primary disease of the nervous system.

inability to swallow, and pa ... of the cases proved fatal and at n ... ffected.

... *reticularis* ... I have also ... n due to polio-myelitis. Inasmuch as the lesions of poliomyelitis cause destruction with loss of function of the involved parts of the nervous system, the hypertension in these cases must be due to either damage to a hypothetical vasodilator center or to parts of the nervous system which inhibit the vasomotor center

Transverse Myelitis.—In patients with lesions of the upper dorsal or cervical cord, hypertension may occur (Thompson and Whitham[295]), usually in conjunction with "spinal reflex sweating" and other manifestations ... high as 240 ... Distention of the bladder ... provoke the pressor crisis (Thompson and Whitham).

Tabes.—Paroxysmal hypertension may occur in tabes. Bennett and Hyman[296] and others have observed cases in which the paroxysms were so severe that the patient was explored for nonexistent pheochromocytoma. It was formerly thought that the paroxysm of hypertension is associated with a gastric crisis and perhaps due to the pain. However, Bennett and Hyman observed hypertension not associated with gastric crisis or other pain and believe the paroxysm due to some as yet obscure autonomic ... pressure regulation.

... paroxysmal and continuous hypertension following cerebral concussion have been described (Raab[297]). However, hypertension of this causation appears to be very rare, and that it ever becomes permanent remains to be demonstrated. Raab attributed the hypertension in his 2 cases to injury to the upper medulla oblongata and obtained pharmacologic evidence of hyperirritability of the vasomotor centers

Post-Diphtheritic Paralysis.—Hypertension has also been observed in ... h severe ... sympathectomy, in whom necropsy revealed a small pedunculated tumor in the fourth ventricle

Hypothalamic Lesions.—Heinbecker[300] has described atrophy of the paraventricular hypothalamic nuclei as the basis of some cases of Cushing's

stein hold it to be. Since Page and his associates find that experimental hypertension due to either perinephritis or buffer nerve section is likewise inhibited by 1-hydrazinophthalazine, as is sometimes essential hypertension (page 881), the question of the rôle of a cerebral humoral mechanism in human hypertension arises. As yet, however, there is no evidence that such is the case.

Neurogenic Hypertension in Disease of the Central Nervous System.—*Increased Intracranial Pressure.*—An unequivocal example of hypertension due to alteration in the activity of the vasomotor center is that which results from increased intracranial pressure due to brain tumor or other expanding intracranial lesion. The classical experiments of Cushing[283] showed that compression of the medulla leads to immediate rise in the general blood pressure. That the hypertension of increased intracranial pressure emanates from the medulla is proved by Forster's[284] finding that it develops after segregation of the medulla and pons from the structures rostral to them. Anrep and Starling[285] long ago showed experimentally that "changes in the blood pressure in the vasomotor center produce the reverse changes in the blood pressure in the rest of the body." The conception that the [illegible] due to ischemia [illegible] Kety[286] and his a[illegible] ing cerebral blood flow, they showed in 13 patients with brain tumor that the rise in cerebrospinal fluid pressure is associated with increased cerebrovascular resistance and, when the pressure exceeds 450 mm. of water, decreased cerebral blood flow. The same was found by Ferris[287] by another method. Basically a similar mechanism, anoxia of the vasomotor center, is apparently responsible for the hypertension that results from asphyxia. Possibly, the hypertension produced by anoxia of the vasomotor center is due to local accumulation of waste products, for perfusion of the medulla with an acid fluid produces hypertension (Roberts[288]) It is also probable that anoxia sensitizes the vasomotor center to the carbon dioxide of the blood. The same factors may be concerned in the so-called high pressure stasis (Chapter 26).

Attempts have been made to produce protracted hypertension by other methods of decreasing blood flow through the medulla Thus, by blocking the outflow of the cerebrospinal fluid in dogs by the intracisternal injection of kaolin, Dixon and Heller[289] evoked elevation of blood pressure which lasted for months. Nowak and Walker[290] and Fishback[291] *et al.* induced hypertension in dogs by ligation of the major arteries to the head (carotid, vertebral, spinal). However, Taylor and Page[292] found that hypertension was produced by this method in only 24 per cent of the surviving animals and lasted only seven to fifteen days. By combining ligation of the cephalic arteries with thermal and mechanical stimulation from a tantalum wire in the floor of the fourth ventricle heated by diathermy, Taylor and Page produced hypertension which lasted as long as two to ten months. Since they found that the effects on blood pressure of medullary ischemia and the stimulation from the tantalum wire were additive, they believe that the hypertension of increased intracranial pressure is due not only to decreased medullary blood flow but also to the mechanical pressure of high cerebrospinal fluid tension.

... excitable state of the vasomotor centers in essential hypertension. ... three times as great a ...

... of the carbon dioxide tension of the ... pressure in essential hypertension but not in normal controls. Since these effects were not obtained in hypertension induced by epinephrine, Raab believes that they are of central origin, a corollary that, while quite probably true, does not follow unconditionally from the evidence presented. Raab also found that in nephritic hypertension the reactions to carbon ... were the same as in normals. His ...

... on the blood pressure patients with essential ... In a subsequent investigation, Raab reaches the conclusion—largely on the basis of the already known facts, which he verifies, that oxygen want and acid perfusion stimulate the medullary vasomotor centers—that essential hypertension results from spasm or sclerosis of vessels in the brain stem so that local oxygen want and accumulation of lactic acid result ...

A number of investigators have described lesions in the region of the vasomotor center in the medulla in essential hypertension. Riebold[304] studied a case of hypertension of twenty years' standing in which necropsy revealed no ... sclerosis with a ... in the vessels a ... are responsible ... he presented no convincing support ... changes in the ganglion cells in the region of the vasomotor center in 5 instances of hypertension. Bordley and Baker[306] also observed arteriosclerotic changes in the small vessels of the medulla in individuals with persistent hypertension. On the other hand, in a later exhaustive investigation, Cutler[307] found that in more than one-half of the cases with hypertension, sclerosis of the vessels in the medulla is absent. Ruehl[308] also found no evidence that the medulla oblongata in hypertensive individuals suffers notably from deficient circulation; he observed the region of the vasomotor center to be morphologically intact. And Baker's[310] studies showed that, while the larger cerebral arteries often present definite arteriosclerotic narrowing, the average small cerebral artery in long-standing essential hypertension shows little change; only when the process enters the malignant phase do the small cerebral arteries show intimal and medial alterations. Likewise, the writer[311] found arteriolosclerosis in the brain in only 6 of 31 cases of long-standing essential hypertension, however, only a few areas were examined in each case.

It does not seem that adequate evidence has been presented that organic lesions of the blood vessels supplying the vasomotor center are the cause of ...

syndrome, including hypertension. It was mentioned above that hypertension has been produced by damaging the hypothalamus. However, the observations of Birchall *et al.*[301] on the diuretic response to injected saline afforded no evidence of impaired hypothalamic function in essential hypertension.

Participation of the Central Nervous System in Essential Hypertension.—In many patients with essential hypertension, especially in the clinically early stages, symptoms plausibly attributed to a cerebral origin dominate the picture. Most often, the symptoms in question closely resemble those of a psychoneurosis, such as restlessness, irritability, emotional instability, fleeting headache, sweating, flushing, palpitation, coldness of the extremities, etc. Page pointed out that in some cases the clinical picture is one that can be explained on the basis of diencephalic stimulation (page 800). In most patients in the early stages of essential hypertension, not only the subjective symptoms but also the blood pressure show great fluctuations with periods of seeming normality. Moreover, both symptoms and blood pressure are often influenced by emotion.

These clinical observations suggest a nervous origin of essential hypertension and have led to the widespread designation as *neurogenic hypertension* of essential hypertension in which the nervous symptoms are prominent. The appelation neurogenic hypertension has also been applied to the earlier, fluctuant stages of essential hypertension regardless of whether or not symptoms are present. That neurogenic hypertension actually exists is demonstrated by the hypertension in the organic diseases of the central nervous system mentioned in the preceding section, by the emotional hypertension to be discussed below, and by the experimental hypertension following section of the moderator nerves. But that the same is true of essential hypertension still has in it an element of assumption A [illegible]

[illegible] origin. Similar symptoms are often present during the climacteric and yet their relief by an estrogen testifies to their endocrine and not nervous origin; actually, a considerable proportion of the cases designated as neurogenic hypertension are women in the climacteric period While it is quite probable that a large contingent of the cases included in the concept of essential hypertension originate in the nervous system, this has not yet been proved beyond doubt, and until such proof is forthcoming the application of the term neurogenic hypertension to patients with essential hypertension is not beyond cavil

Probably largely influenced by the evidence that the hypertension of increased intracranial pressure is due to stimulation of the vasomotor center, various investigators have regarded essential hypertension as originating in alterations in this part of the brai [illegible] advanced by Monakow,[302] who, with [illegible] hypertension to a disturbance in the [illegible] the vasomotor centers are hyperirritable and "set" at a higher level, much as the thermo-regulatory centers are thought to maintain the body temperature at a higher level in fever. In harmony with Monakow's hypothesis are the observations of Raab,[303] who believes that his experiments indicate

block of the carotid sinus produces in normotensives an average rise in

nerves are thus proved
the elevation in intra-
rate through the carot...

same as in normotensives and the stimulation of the carotid sinus receptors is consequently the same.

The suggestion that arteriosclerotic changes in the arch of the aorta and the carotid sinus might produce hypertension is not supported by the investigations of Keele,[340] who found no relation between the degree of arteriosclerotic involvement of the carotid sinus and aorta and the presence of hypertension

Although there is thus no evidence that essential hypertension originates as a disorder of the autonomic nervous system, many formerly took for granted that, whatever the origin of essential hypertension, the arteriolar *constriction* which is the immediate mediator of the rise in pressure is produced by augmented tone of the sympathetic vasoconstrictor nerves. Such sympathetic stimulation is responsible for the neurogenic hypertension produced by increased intracranial pressure or section of the moderator nerves, for in both sympathectomy lowers the blood pressure to

ponent of the mechanism of renal hypertension, for the latter is not prevented or abolished by sympathectomy (page 321) or dibenamine or other adrenergic blocking agents (Wilburne[344] *et al*, Katz and Friedberg[345]).

Contrary to what might have been anticipated, the results of sympathectomy ...

... lowers the blood pressure in only some patients with essential hypertension, and in almost all of these the blood pressure subsequently rises The same is true of sympathetic blocking agents (Chapter 29). Moreover in those ...
pressure,
be compl...
that rela... of the postarteriolar stream bed decreases the venous return to the heart The results of sympathectomy and sympathetic blocking agents therefore do not afford an unequivocal assessment of the

is often found where there was no hypertension during life. And it has been seen that arteriolosclerosis is quite probably a concomitant or consequence of hypertension; there is no reason to assume that such lesions in the cerebral arterioles have any different pathogenesis than in other organs. Moreover, they are frequently completely absent in essential hypertension.

There seems to be no evidence that the proliferative and degenerative changes in the cerebral capillaries described by Scheinker[331] in essential hypertension cause the rise in blood pressure; the writer doubts their specificity and believes they are far from constant.

To summarize what is known about the causation of hypertension by organic lesions of the central nervous system: *Observations in bulbar poliomyelitis and other diseases prove that organic lesions of the central nervous system can produce severe and protracted hypertension. But the existence of such lesions in the usual essential hypertension has not been demonstrated.* Of course, this does not prove that the lesions do not exist; the field is in urgent need of further investigation by modern neurohistological methods. Nor is there evidence that cutting down of cerebral blood flow by arteriosclerosis or arteriolosclerosis plays a causative rôle in essential hypertension.

The Autonomic Nervous System.—Because of the great importance of the vegetative nervous system in the physiological regulation of the circulation, it has often been thought that essential hypertension might originate in this system. Da Costa and Longstreth[334] long ago claimed to have found lesions of the sympathetic ganglia in Bright's disease which they believed to be responsible for the renal lesions and cardiac hypertrophy. So far as I am aware, these findings were never confirmed Dember's[335] histological studies of the splanchnic nerves and sympathetic ganglia removed at 20 sympathectomies on hypertensive patients disclosed no abnormalities. Contrary to some earlier findings of increased cholinesterase activity of the serum in hypertension, which had been interpreted as evidence of autonomic imbalance, Vorhaus[336] found the cholinesterase activity normal.

Following the discovery of the enormous importance of reflexes originating in the carotid sinus and arch of the aorta for the regulation of the blood pressure (page 303), the possibility that hypertension results from derangement of this reflex mechanism had to be taken into consideration. We have already referred (page 304) to the important work of Koch and Mies, who produced chronic hypertension in animals by severing the afferent nerves from the aorta and carotid sinus; other investigators have since accomplished the same. However, there is no evidence that this form of experimental hypertension has any relation to essential hypertension in man.

While the rise in blood pressure in essential hypertension is the result of arteriolar constriction and not of increased cardiac output, that in section of the moderator nerves seems to be due primarily to increase in cardiac output. Carotid sinus hypertension, contrary to the essential variety, is always accompanied by extreme tachycardia It was seen on page 304 that external pressure on the carotid sinus has much the same effect on normotensives and hypertensives. Indubitable evidence that the function of the carotid sinus nerves is intact in hypertension is afforded by the experiments of Lampen[337] and his co-workers. They found that bilateral procaine

panied by fall in pressure. Wolff *et al.* further observed that when anxiety and conflict are evident and overt, the rise in pressure is due to increased cardiac output; while when the *manifestations* of conflict are suppressed both peripheral vasoconstriction *and augmented* cardiac output participate in the pressor response. The second pattern with vasoconstriction is characteristically invoked by patients with essential hypertension. It is interesting that, contrary to emotional stress, physical exercise does not elevate the blood pressure more in hypertensives than in controls (Taylor ... Wolff found that both normotensives and hyper-

fundamental observations of Wolff and his associates show that ... normals and hypertensives react to emotional stress with the same circulatory pattern of response—rise in blood pressure with decreased renal blood flow—but the intensity and duration of the reaction is greater in the hypertensive

2. *Overtly Emotional Initiation or Aggravation of Clinical Hypertension.*— A variety of clinical observations shows that emotion may initiate hypertension of more than momentary duration or aggravate pre-existent hypertension In some, though apparently exceptional, instances of depressive states in insanity, there is marked hypertension, which may disappear with recovery from the melancholia (Mueller). I have also seen such cases. Patients with essential hypertension, as do so many with other diseases, often state that their symptoms appeared after an emotional upset It is a fairly common clinical observation that, in patients with

ing from an emotional state was long ago published by O. Mueller[223]

A man of "pyknic-arthritic" habitus entered the clinic with a systolic blood pressure of 280 mm and occasional attacks of pulmonary edema. Corresponding to the stasis, there was a trace of albumin in the urine and diuresis was deficient (bed-rest and the usual chemical means were without effect). One day, the man, who was of a very amiable nature stated that he had behaved unfairly to his wife, and this situation depressed him ... the ...) to ... ary ... son without any deleterious consequences. The excretory functions of the kidney were perfectly normal Mueller saw the patient several years later and found him healthy with a blood pressure of 130 mm, though the cardiac hypertrophy had not completely disappeared

Observations on large groups subjected to intense emotional trauma ... se in arterial pressure of more ... [224] examined 695 men from an ... ear of desert warfare, between ... , he found that 27 per cent had ... er 100 mm. Reëxamination of

neurogenic element. For the same reason, the study of the effect of high spinal anesthesia in essential hypertension (Gregory and Levin,[318] Taylor[319] *et al.*) does not offer an index of neurogenic participation.

Strong evidence that the tone of the sympathetic vasoconstrictor nerves is not increased in essential hypertension is afforded by the pioneer experiments of Prinzmetal and Wilson[346] and Pickering.[347] These investigators measured plethysmographically the blood flow through the hand before and after the activity of the sympathetic nerves had been eliminated by nerve block or warming. The increase in blood flow following elimination of the action of the sympathetic nerves was no greater in the hypertensives than in the controls. This indicates that the sympathetic tone in the hand is not augmented in essential hypertension, else the blood flow would have increased more on elimination of this tone than in controls.

This fundamentally important finding of Prinzmental and Wilson and Pickering—that the tone of the sympathetic vasoconstrictor nerves is not increased in essential hypertension—has recently been buttressed by an independent method by Kowalski[401] *et al.* They showed that the effect of tetraethylammonium on peripheral resistance depends on the vasomotor tone, and use of this test discloses no increase in neurogenic vasomotor tone in the extremities of hypertensive subjects.

Psychic Factors in the Production of Essential Hypertension.—Many recent investigators have arrived at the conclusion that psychic factors play an important, according to some, predominant, rôle in the causation of essential hypertension. This point of view was forcefully pioneered by Moschcowitz[312] as far back as 1919. Since then, it has been supported by Alexander,[313] Weiss,[314] Wolff,[315] Binger,[316] Dunbar,[317] and many other investigators of the rôle of the psyche in disease of the soma With the rise of the concept of psychosomatic disease in the past two decades, the interpretation of essential hypertension as a paradigm of such a disease has gained more and more advocates—among internists as well as psychiatrists Principal among the lines of evidence regarded as favoring the psychosomatic theory of the genesis of essential hypertension are the following.

1. *The Pressor Effects of Emotion.*— It has long been known that various emotions and other mental processes may produce transitory or even long-continued elevations in blood pressure Bickel[318] found that mental work, intellectual pleasure and displeasure, sensual pleasure and displeasure, and strained attention all cause a rise in blood pressure, if they produce any change at all Stieglitz[319] reported a series of cases in which emotional strain was accompanied by hypertension On the other hand, Fischer[320] found that mental exertion unaccompanied by an emotional element, as in the solution of difficult chess problems, had no notable effect on the blood pressure.

Outstanding studies of the effects of emotion on the blood pressure and other circulatory variables have been carried out by Wolff[315] and his associates. They find that the blood pressure rises when the normal or hypertensive subject, in a stressful interview, is resentful because he considers himself menaced or trapped. Contrariwise, what seems very exceptional in the hypertensive, the feeling of being overwhelmed is accom-

Wolff *et al.* further observed that when anxiety

both peripheral vasoconstriction and augmented cardiac output ... pate in the pressor response. The second pattern with vasoconstriction is characteristically invoked by patients with essential hypertension. It is interesting that, contrary to emotional stress, physical exercise does not elevate the blood pressure more in hypertensives than in controls (Taylor ... and that both normotensives and hyper-

fundamental observations of Wolff and his associates ... normals and hypertensives react to emotional stress with the same circulatory pattern of response—rise in blood pressure with decreased renal blood flow—but the intensity and duration of the reaction is greater in the hypertensive.

2 *Overtly Emotional Initiation or Aggravation of Clinical Hypertension.*—A variety of clinical observations shows that emotion may initiate hypertension of more than momentary duration or aggravate pre-existent

cases Patients with essential hypertension, as do so many with other diseases, often state that their symptoms appeared after an emotional upset It is a fairly common clinical observation that, in patients with

> A man of "pyknic-arthritic" habitus entered the clinic with a systolic blood pressure of 280 mm and occasional attacks of pulmonary edema. Corresponding to the stasis, there was a trace of albumin in the urine and diuresis was deficient (bed-rest and the usual chemical means were without effect) One day, the man, who was of a very amiable nature stated that he had behaved unfairly to his wife, and this situation depressed him extremely In the hospital, everything was successfully explained to the wife, which resulted in the systolic blood pressure dropping from 280 to 150 mm, the diuresis becoming satisfactory, disappearance of pulmonary edema and proteinuria, and the patient moved about like a healthy person without any deleterious consequences The excretory functions of the ... ent several years ... mm, though the

Observations on large groups subjected to intense emotional trauma show that many of those affected develop rise in arterial pressure of more than momentary duration When Graham[324] examined 695 men from an Armoured Brigade, who had had at least a year of desert warfare, between four and eight weeks *after* battle had ceased, he found that 27 per cent had asymptomatic diastolic hypertension of over 100 mm. Reexamination of

33 of these hypertensives after two months more freedom from battle anxieties revealed 28 to have a normal blood pressure. Ehrstrom[325] observed that about one-quarter of front line soldiers on the Finnish front had a systolic pressure of over 150 mm. and that over half of these had an elevated diastolic pressure. After the Texas City blast disaster, Ruskin *et al.*[326] observed that 103 of 180 injured had a diastolic pressure of over 95 mm. at one time or another; the hypertension seems to have been of brief duration but in extreme cases reached a diastolic level of 140 to 160 mm.

3. [illegible] found that 10 of 12 rats subjected to a minimum of 167 daily exposures to the sound of an air blast developed hypertension, while the latter appeared in only 1 of 11 controls. The rats had been tested for emotionality, and it was found that while all the emotional air-blasted rats [illegible] essential hypertension.

4. *The Personality of the Patient with Essential Hypertension.*—Many who have studied hypertensive patients from a psychological point of view have thought that their observations disclosed a specific type of personality with a characteristic reaction pattern in interpersonal relations as especially prone to develop essential hypertension. Unfortunately, the characterizations of the "hypertensive personality" have differed. Thus, Gressel *et al.*[328] cite different investigators who regard the hypertensive personality as characterized by habitual unexpressed or displaced hostility, lifelong emotional lability with frequent depression, anxiety or both, lifelong anxiety, perfectionism, compulsiveness, or difficult with authority. Moschcowitz[312] originally described the hypertensive individual as the antithesis of the child in mind and spirit; "they do not play, they are irritable and have single-track minds without avocations. While their mental horizon is narrow, within this range they are tense and pursue their aims with a grim desperation." Weiss, one of the earliest protagonists of the importance of emotional factors in the causation of essential hypertension, finds that chronic and repressed rage and anxiety are especially important. Menninger[329] believed that suppressed resentment, hate or fear is of great importance in the causation of essential hypertension The large majority of Binger's hypertensives had great difficulty in asserting themselves Wolf and Wolff found that their "hypertensive subjects, often gentle, poised and apparently easy going, were filled with aggressive drive, which was tightly restrained by a need to please " Palmer[330] observed in his studies of the personalities of 50 hypertensives that "Originality, special skills and even special interests are conspicuous by their absence. Practicality, objectivity and adaptability are the chief characteristics. The predominant character traits which the physician sees and which the patient recognizes in himself are those with survival value in our competitive cash culture." Gressel and his associates have investigated the correlation between certain personality patterns and hypertension. They found statistically significant degrees of association with hypertension for "obsessive-compulsive behavior" and "subnormal assertiveness."

5. *The Early Symptoms.*—Emotional instability, restlessness, irritability and, in ... ontrate are sometimes among the first sym... physicia... that most of the early symptoms of essential hyperten... ...tions of the psychoneuroses. The latter ...

Var... ... amo... rece... that they are ...

6. *Occurrence of Essential Hypertension in Advanced ...*—... been seen (page 691) that essential hyperten on is largely a disease of *advanced cultures.* This has been attributed to the complex interpersonal relationships characteristic of contemporary Occidental civilization and regarded as compatible with a psychosomatic genesis of essential hypertension

7 *Improvement as a Result o...* ... of symptomatic improvement ... tensive patients under psychotherapy ... to improvement in the emotional status of the patients when anxiety is ... extroversion of repressed hostility (Weiss). Wolff ...

one-tenth was accompanied by reduction of blood pressure to ... levels for significantly long periods

... patients with essential ... ly during sleep and after ...

... is directly in the ... e of the supporting evidence just cited is highly suggestive But there are also strong objections

... been impressed by the extreme rarity of ground for the belief that the hypertension had been initiated by a clearly defined psychological reaction. Indeed, although a high proportion of the patients whom I see in private practice give what seems to me an intelligent anamnesis, and notwithstanding careful inquiry into the life situation of each patient, I have yet to encounter an instance in which the psychogenic initiation of essential hypertension was unequivocal.

33 of these hypertensives after two months more freedom from battle anxieties revealed 28 to have a normal blood pressure. Ehrstrom[325] observed that about one-quarter of front line soldiers on the Finnish front had a systolic pressure of over 150 *mm.* and that over half of these had an elevated diastolic pressure. After the Texas City blast disaster, Ruskin *et al.*[326] observed that 103 of 180 injured had a diastolic pressure of over 95 mm. at one time or another; the hypertension seems to have been of brief duration but in extreme cases reached a diastolic level of 140 to 160 mm.

[illegible]

[illegible] found that 10 of 12 rats subjected to a minimum of 167 daily exposures to the sound of an air blast developed hypertension, while the latter appeared in only 1 of 11 controls. The rats had been tested for emotionality, and it was found that while all the emotional air-blasted rats developed hypertension none of the emotional controls did. The blast hypertension developed only in the older rats, which is a similarity to human essential hypertension.

4 *The Personality of the Patient with Essential Hypertension*.—Many who have studied hypertensive patients from a psychological point of view have thought that their observations disclosed a specific type of personality with a characteristic reaction pattern in interpersonal relations as especially prone to develop essential hypertension. Unfortunately, the characterizations of the "hypertensive personality" have differed Thus, Gressel *et al.*[328] cite different investigators who regard the hypertensive personality as characterized by habitual unexpressed or displaced hostility, lifelong emotional lability with frequent depression, anxiety or both, lifelong anxiety, perfectionism, compulsiveness, or difficult with authority Moschcowitz[312] originally described the hypertensive individual as the antithesis of the child in mind and spirit, "they do not play, they are irritable and have single-track minds without avocations. While their mental horizon is narrow, within this range they are tense and pursue their aims with a grim desperation." Weiss, one of the earliest protagonists of the importance of emotional factors in the causation of essential hypertension, finds that chronic and repressed rage and anxiety are especially important. Menninger[329] believed that suppressed resentment, hate or fear is of great importance in the causation of essential hypertension. The large majority of Binger's hypertensives had great difficulty in asserting themselves Wolf and Wolff found that their "hypertensive subjects, often [illegible] going, were filled with aggressive drive [illegible] need to please." Palmer[330] observe[illegible] 50 hypertensives that "Originality, special skills and even special interests are conspicuous by their absence. Practicality, objectivity and adaptability are the chief characteristics. The predominant character traits which the physician sees and which the patient recognizes in himself are those with survival value in our competitive cash culture." Gressel and his associates have investigated the correlation between certain personality patterns and hypertension They found statistically significant degrees of association with hypertension for "obsessive-compulsive behavior" and "subnormal assertiveness."

The psychosomatic theory of essential hypertension has not graduated from the status of a theory. Various emotions occasion elevation of blood pressure in both the healthy and hypertensives. In addition to raising the blood pressure, they may precipitate or aggravate symptoms in essential hypertension. But that repeated pressor episodes of emotional origin can ultimately induce a self-perpetuating hypertensive mechanism [illegible] disturbed interpersonal relationship or

[illegible]

As yet, the rôle of the nervous system, [illegible] tial hypertension remains shrouded in darkness

ESSENTIAL HYPERTENSION AND SELYE'S ADAPTATION SYNDROME

Selye's[350] brilliant studies have brought evidence that *any* stress affecting large portions of the body elicits—in addition to the specific damage and reaction characteristic of the individual noxious agent—essentially similar functional, biochemical and morphological changes in the vertebrate organism The totality of these nonspecific changes he calls the *General Adaptation Syndrome* Among the "stresses" which Selye studied, and on the basis of which he developed his concept of the General Adaptation Syndrome, are cold, fatigue, infection, intoxication and emotion As the designation indicates, Selye believes the General Adaptation Syndrome is a coordinated, useful response participating in the defense of the threatened organism The General Adaptation Syndrome is initiated by stimulation of the hypophysis and the hypothalamic vegetative centers. The mechanism of the mediation of the stimul [illegible] hypophysis and hypothalamus is unk[illegible] calls into play a hormonal defense [illegible] which in turn results in liberation o[illegible] important rôle in resistance. The hypothalamic stimulation unleashes a nervous defense mediated by autonomic nerves, including discharge of epinephrine and nor-epinephrine from the chromaffin cells. The manifold manifestations of *the nervous and hormonal stimulation* constitute the General Adaptation Syndrome

Selye believes that intensification, protraction or perversion of the primarily beneficent reactions of the General Adaptation Syndrome are the essential elements in the pathogenesis of many common diseases. He terms these *diseases of adaptation* Included are notably rheumatic, allergic, hypertensive and arteriosclerotic maladies, as well as peptic ulcer and perhaps psychosomatic disorders In all of these, constituting the [illegible] tion, [illegible] rmal [illegible] and

2. The writer has not been able to differentiate the "hypertensive personality." The descriptions of the personality of the hypertensive patient given by advocates of the psychosomatic theory differ from one another; the characteristics they describe are absent in many hypertensives and present in numerous normotensives. Suppressed resentment, hate and fear—most often described as characteristic of the hypertensive personality—are found in victims of peptic ulcer and many other diseases quite as well as in hypertensives.

3. The fact that, contrary to such diseases as peptic ulcer and Graves' disease, established essential hypertension almost never undergoes spontaneous cure not only does not support a primarily psychogenic origin of the disease but is difficult to reconcile with the latter. This is all the more significant because well established essential hypertension may exist for a decade or more without evidence of irreversible morphologic changes in the kidneys or other organs.

4. While emotion may occasion a rise in blood pressure, there is no evidence that the pressor mechanism thus set in action is self-perpetuating. In the observations of Graham cited above, in which hypertension was the result of a year or more of campaigning in the African desert, within a few months the blood pressure of almost all the subjects had returned to normal.

5. In the hypertensive patients seen by the writer who have undergone psychotherapy, the effect on the natural history of the disease has not been such as to indicate a primarily psychoneurotic origin. The fact that a judicious physician can often attain symptomatic relief in essential hypertension by reassurance and other forms of suggestion—and that with the reassurance of the patient the blood press [illegible] not prove that the disease is primarily of [illegible] help afforded by reassurance in a host of di[illegible] would indeed be a burden. The fall in blood pressure during sleep or after sedatives does not indicate the psychogenic nature of essential hypertension; it occurs in health and I have observed it in nephritic hypertension.

The psychosomatic theory of essential hypertension is still *sub judice*. There may be included in our present ill-defined concept of essential hypertension cases of psychogenic nature. But the evidence available at present does not indicate that, in at least the vast majority of cases of essential hypertension, disturbances in interpersonal adjustment play more than a secondary and aggravating rôle

Summary.—Protracted hypertension may have its origin in the nervous system. Interruption of the moderator nerves, appropriately situated lesions of the central nervous system, and interference with the blood flow through the medulla may each call forth neurogenic hypertension. However, there is no evidence that any of these mechanisms plays a primary part in the pathogenesis of essential hypertension. Nor has it been demonstrated that essential hypertension is mediated through increased tone of the vasomotor nerves The finding that essential hypertension may persist after as complete a sympathectomy as feasible indicates that participation of the nervous system is not a *sine qua non* for the perpetuation of the disease.

observe hypertension in rabbits given lead. Contrariwise,
with lead. In rats, Griffith and
survived the ad-

-les of lead poison-
ing. According to Vaquez,[355] Stoll had observed in the eighteenth century that the pulse is very hard during lead colic. At the time that plumbism was very common, Pal,[356] Vaquez and others found that hypertension often accompanies lead colic. I observed the same association; the hypertension was not due solely to the pain, for it was present when the latter was controlled. Traube[357] noted and Vaquez confirmed that lead encephalopathy occurs almost invariably in the presence of marked hypertension. In an instance of lead encephalopathy observed by Ménetrier,[358] the systolic pressure reached 300 mm. There is evidence that acute lead hypertension is due to vasoconstriction. Elschnig[359] observed ophthalmoscopically the obliteration of the retinal arteries in a painter who became

pressure was lowered by amyl nitrite. Vaquez and Pal interpret their observations as indicating that lead colic is the result of spasm of the mesenteric vessels with ischemia of the intestine, though it is also possible that the colic is primarily due to spasm of the intestinal musculature. Tscherkess[360] showed in rabbits that lead stimulates the smooth muscle of the vessel wall

Older observers described a high incidence of hypertension in chronic
tension the rule in chronic
in 39 per cent of painters
[363] pointed out in 1863 that
proteinuria and granular kidneys are common in chronic plumbism Dickinson[364] found that of 42 workers in lead trades who died from disease or accident, 26 had granular kidneys. The lesions appear to be the results of arteriolosclerosis (cf Brogsitter and Wodarz[365]).

were actually instances of essential hypertension which had no connection with the exposure of the patient to lead However, some of the difference between older and more recent observations on the occurrence of hypertension and renal disease as a result of plumbism may well be due to the

animals by exposure to cold and other forms of "nonspecific stress," and by the injection of adrenal cortical steroids or the stimulation of their formation by pituitary hormones. In rats, after preliminary unilateral nephrectomy and the use of 1 per cent NaCl as drinking water, Selye found that desoxycorticosterone acetate produces hypertension, cardiac hypertrophy, arteriolar lesions ranging from hyalinization to periarteritis nodosa, and nephrosclerosis with glomerular hyalinization. Similar effects were readily elicited in young chicks. Contrariwise, hypertension and arteriolar lesions were produced by this procedure only irregularly and with large doses of DOCA in the dog, guinea pig, hamster, monkey, mouse and cat. Selye found that administration of DOCA to rats on a sodium-free diet does not result in hypertension, vascular lesions or nephrosclerosis. Selye believes that DOCA produces hypertension largely through the intermediacy of the kidney; he cites experiments in which such hypertension in the rat is prevented by bilateral nephrectomy (*cf.* however, page 710).

On the basis of these and many other considerations (pages 558-576 of his recent book[390]), Selye believes that most clinical forms of hypertension are due to excessive stimulation by various types of stress of the normal adaptive reactions of the body which constitute his General Adaptation Syndrome. The stress produces the hypertension through the intermediacy of ACTH and adrenal cortical steroids, or it may result through nervous mechanisms with adrenergic stimulation.

Selye's conception of essential hypertension as an exaggeration of the normal defensive mechanisms which he collectively terms the General Adaptation Syndrome is closely allied to the psychosomatic theory of the disease. It constitutes an integration of beliefs held by many in various forms that aberrations in the activities of the adrenal cortex, the adrenal medulla, the adeno-hypophysis or the autonomic nervous system call forth the rise in arterial pressure. The evidence summarized in the preceding sections indicates that the part played by these organs, individually or collectively, in essential hypertension has not been established. That essential hypertension is actually an exaggeration or perversion of the same pituitary-adrenal or hypothalamic-autonomic mechanisms which participate in the normal defense against stress also remains to be demonstrated. Nevertheless, the suggestion constitutes a thought-provoking working hypothesis and may help canalize research along fruitful lines.

MISCELLANEOUS AGENTS WHICH HAVE BEEN CONSIDERED IN RELATION TO THE ETIOLOGY OF ESSENTIAL HYPERTENSION

Lead.—Clinicians of former generations accepted lead among the causes of Bright's disease. In recent years, however, the causation of hypertensive and renal disease by plumbism has been seriously questioned. In this connection it should be borne in mind that lead poisoning has decreased enormously in frequency in recent years; I have not seen lead encephalopathy in twenty years. Nevertheless, there seems little doubt that lead was formerly incorrectly incriminated in many instances of hypertensive disease.

. . . t the cases of

pointed . . .
. . . with renal disease was greater than in . . . of alcohol in the

persons with occupations less predisposing to . . .
careful survey disclosed no evidence that alcohol is deleterious to the
ki

as due to alcoholism . . .
trophy"—the Munich "beer heart" and the Tuebingen "wine heart"—
which are now known to have been instances of essential hypertension.
But it must be remembered that in these cases the chronic alcoholism was accompanied by excessive ingestion of food and fluid usually resulting in obesity, all of which are factors that may play a part in bringing out hypertension in predisposed individuals. It is, *therefore*, far from evident that alcohol as such played any part in causing the hypertension in these cases of beer and wine heart.

Most later authors attribute little or no significance to alcohol *per se* in . . . is a factor . . . Allbutt[354]

most of them elderly men at the time of life when essential hypertension appears, but the tendency was to low rather than high pressures. Nor is

able to alcohol. Most often, alcoholics have good kidneys and blood-vessels, though the kidneys are often rather large, presumably hypertrophy due to increased work and akin to the renal hypertrophy of animals on protracted high-protein diet.

Intestinal Auto-intoxication.—Huchard[355] thought that the absorption of toxic substances from the intestine plays a large part in the production of essential hypertension, and early in this century a voluminous literature on the subject accumulated, which will be found summarized in Allbutt's[354] book. It is true that pressor amines are formed in the bacterial putrefaction of protein and that certain quantities of such substances are present in the intestinal contents. But so far as I am aware, there is no tangible evidence for the attractive hypothesis, which Abel[357] thought might lead to the solution of important problems of vascular and renal pathology, that intestinal auto-intoxication is concerned in the pathogenesis of essential hypertension. This conclusion is substantiated by the statistical investiga-

modern protection of workers in lead industries. Formerly chronic lead poisoning was very common. Nowadays, it has become rare as a result of the precautions taken. Moreover, if a worker develops any indication of plumbism he is promptly removed from further exposure. Formerly, the victims of chronic lead poisoning returned again and again to their work. In New York City, at present, lead intoxication is of negligible significance in the causation of hypertension and renal disease.

Tobacco.—Huchard[368] ranked tobacco prominently among the causes of hypertension, and high blood pressure was formerly one bogie flaunted by the anti-smoking propagandists. Nevertheless, there is no convincing evidence that smoking contributes to the production of chronic hypertension. It is true that in pharmacological experiments nicotine raises the blood pressure through stimulation of both the vasoconstrictor center (Pilcher and Sollmann[369]) and the peripheral autonomic ganglia (Hoskins and Ransom[370]). Dixon[371] found that the smoking of a Manila cigar by a novice causes a rise of 20 to 25 mm. in systolic pressure, which is followed after one-half hour by a sharp fall. In veteran smokers, however, he found that smoking has little effect on the blood pressure. John[372] noted a rise in diastolic pressure after the smoking of 2 cigars or 10 cigarettes. Mathers *et al.*[373] observed that in habitual smokers smoking 2 standard cigarettes produced an average rise of 14.7 mm. in systolic and 8 mm. in diastolic pressure; the corresponding figures for low-nicotine cigarettes were 11.4 and 5.4 mm. In 6 healthy habitual smokers under basal conditions, Roth[374] found that smoking 2 standard cigarettes was followed by an average rise of 19 mm. systolic and 14 mm. diastolic; smoking corn silk cigarettes or puffing unlighted standard cigarettes had no effect. Hines and Roth[375] found that an especially pronounced rise in blood pressure follows smoking in individuals in whom a hyperreactive vascular system is revealed by an excessive pressor response to immersion of an extremity in cold water.

Despite these transitory effects, the fact that most men who have smoked excessively for many years have normal or even low blood pressure shows that smoking *per se* does not cause hypertension. In fact, Lauder Brunton[376] went so far as to say that "If in a strong healthy man, one found the tension was about 100, or below, and he was told he smoked too much, in 19 cases out of 20 it would be correct." I have also often noted hypotension in inveterate smokers, though, of course, such individuals are by no means immune to hypertension. Thompson and Sheldon[377] found that even in persons with hypertension smoking does not have any uniform effect on the blood pressure, the number of patients in whom smoking decreased the arterial tension not differing greatly from the number in whom the blood pressure rose.

It would, therefore, seem that whatever may be the damage done to the circulatory apparatus by smoking, it is not effected through the medium of hypertension.

Alcohol.—Alcohol, of course, has been reckoned among the causes of essential hypertension, as it has been considered to be at the root of so many afflictions. Bright[378] thought that abuse of alcoholic beverages may play a part in the causation of renal disease, and Christison[379] held

Summarizing, it may be stated that there is no evidence that syphilis has any part in the causation of essential hypertension. Nor is there any evidence that syphilis ever causes hypertension to enter the malignant phase (page 821).

Other Infections.—It was formerly occasionally stated that essential hypertension results from old infections, or is a manifestation of focal infection. There is no evidence for these views. Walker and O'Hare[295] studied the comparative incidence of past infections in 400 patients with hypertension and in 400 hospital inmates with normal blood pressure. There was no notable difference between the two groups. I have never seen any effect on the blood pressure of hypertensive patients from the removal of infected teeth, tonsils or other "foci." It was mentioned above that tuberculosis is uncommon in hypertensive patients, and when it does occur it is usually extremely chronic with great tendency to fibrosis and healing.

Allergy.—Essential hypertension has also been considered to be a mani- [illegible] [296] who observed [illegible] sitive to food [illegible] on removal of the allergens in question [illegible] Bienstock[297] also regards essential hypertension as due to sensitization to animal proteins. On the other hand, Cohen *et al.*[298] found that in 3 hypertensive patients with allergic symptoms, the control of the latter had no effect on the hypertension. In view of the frequency of such allergic diseases as asthma and hay fever as well as of essential hypertension, the occasional association proves nothing. Actually, there seems to be no good evidence indicating that essential hypertension is a manifestation of allergy in the usual sense of the term. It has seemed to me that hay fever, bronchial asthma and other allergic manifestations are less frequent in essential hypertension than in the general population.

GENERAL DISCUSSION OF THE ETIOLOGY OF ESSENTIAL HYPERTENSION

From the above survey, it is seen that, despite countless investigations and a considerable number of facts revealed by them, we are as yet very much in the dark as regards the causation of essential hypertension. However, some progress has been made. The available evidence points to participation of three categories of pathogenetic factors in the causation of essential hypertension.

1. *Genetic Influences.*—In at least the large majority of instances, *essential hypertension arises on the basis of an inherited predisposition.* The [illegible]

characteristic. The more opportunity I have to study the family history of patients with essential hypertension, the more convinced I am that at least most of *them are* genetically preordained to their affliction.

tion of Alvarez *et al.*[388] who found no correlation between constipation and hypertension; in fact, they noted that in women constipation tends to be associated with low blood pressure.

Syphilis.—In older works, syphilis was almost invariably accorded a prominent place among the causes of "chronic interstitial nephritis." Soon after the introduction of the Wassermann reaction, there were many attempts to incriminate lues as an important factor in the etiology of essential hypertension. Thus, Stoll[389] obtained positive Wassermann or luetin reactions in 43 of 50 patients with hypertensive disease. He considered hypertension as one of the commonest manifestations of congenital lues, a view for which there is no evidence whatsoever. Amblard[390] found syphilis in 78 per cent of hypertensive subjects Grenet *et al.*[391] regarded syphilis as a common cause of essential hypertension; they give an exhaustive description of what they term "hypertension artérielle syphilitique solitaire" Gallavardin[392] also considered syphilis among the important causes of hypertensive disease. He pointed to the frequent coincidence of hypertension with syphilitic aortitis, considering both the aortic and the renal lesions of syphilis causation (*nephro-aortite syphilitique*). Fahr[352] believed that some cases of the malignant phase of essential hypertension (his malignant sclerosis) are of syphilitic origin. He found evidence of lues in 10 of 40 cases of malignant sclerosis, though the Wassermann reaction was negative in 4 of these 10.

Despite these findings, I find no actual evidence that syphilis plays any part in the causation of essential hypertension At the Montefiore and Mount Sinai Hospitals, I did not find the incidence of positive Wassermann reactions greater in essential hypertension than in the general hospital population. Horme and Weiss[393] found practically the same incidence of syphilis in 666 patients with essential hypertension and 2000 non-hypertensive individuals. Nor does the clinical history or physical examination reveal a notably high incidence of syphilis in hypertensive patients I can confirm Gallavardin's observation that the combination of syphilitic aortitis and true (diastolic) hypertension was formerly not uncommon, there were 12 such cases within less than two years at Mount Sinai Hospital, but this does not prove that the hypertension in these patients was due to syphilis. Almost all the patients with both diastolic hypertension and luetic aortitis were negroes or Puerto Ricans, in whom, at the time, the incidence of syphilis was high In recent years, with the decreasing frequency of syphilis, luetic aortitis has become a rarity in the clinical material I have seen but there is at least as much essential hypertension as ever It is possible, though not proved, that hypertension predisposes to the localization of syphilis in the aorta. I have not seen any effect of antisyphilitic treatment on hypertension in syphilitic subjects, a result which is in substantial agreement with the findings of Levinson,[394] though he states that occasionally the blood pressure does drop somewhat. On rare occasions, amyloid contracted kidney resulting from syphilis leads to renal hypertension, but this has no bearing on the etiology of essential hypertension. It is conceivable that the rare sclero-gummatous disease of the kidney might lead to renal hypertension, but I am not aware of any actual case of this nature.

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the next years will see [illegible]
entities. Then the term essential hypertension, the chief value of which is as a confession of ignorance, will retain only historical significance.

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But important as is the recognition of the genetic element in essential hypertension, it discloses only one aspect of the actual nature of the condition and, apart from hypothetical eugenic considerations, hardly points the way toward solution of the therapeutic problem. What the clinician wants to know is the location and characteristics of the inherited abnormality in structure or function which produces the elevation in blood pressure and how the actual hypertension is precipitated in the genetically conditioned individual.

2. *Environmental Agencies.*—There are strong indications that essential hypertension is at least more common in those living under the conditions of modern Western civilization. What in this culture favors the development of essential hypertension is unknown. [illegible] the possible rôle of the abundant lipid and protein content of the diet which modern industrial civilization affords to a far higher proportion of the population than does any other social structure. The evidence is good that chronic undernutrition decreases the incidence of essential hypertension in a population

3. *Pressor Mechanisms.*—In this chapter evidence has been reviewed suggesting the possibility of renal, endocrine and nervous factors in the pathogenesis of essential hypertension. Another obvious possibility—that of primary disease of the arterioles with increase in their intrinsic state of contraction or reactivity to nervous or humoral pressor influences—has been little studied. In the discussion of each of the foregoing, after presentation of evidence bespeaking its possible participation in essential hypertension, other considerations were adduced militating against its primary pathogenetic rôle in at least some of the cases.

The possibility arises that essential hypertension is not an entity but rather embraces several pathogenetically distinct diseases having in common chronic hypertension and its consequences. Such a pluralistic conception is not without attraction to the clinician. In practice one is often impressed that for years the clinical picture of many patients with essential hypertension mimics a psychoneurosis; in others, each of several members of a hypertensive family has an "apoplectic habitus," the picture is dominated from the start by violent headaches and evidences of cerebral arteriosclerosis, and all succumb to cerebral vascular accidents; still others with essential hypertension have so many stigmata of an endocrine disturbance akin to the Cushing syndrome that one goes to great pains to rule out the latter; and there is a further group of patients with essential hypertension in whom evidence of renal damage is present from early in the course and who quickly go on to renal insufficiency. The nervous system, the endocrine glands, the intrinsic functions of the arterial walls and the kidneys probably all participate in the regulation of the blood pressure, and it may well be that included in "essential hypertension" are discrete conditions initiated by disturbances in each of these regulatory coefficients of the arterial pressure. But despite their differing origin, all of these disturbances would tend toward a common clinical picture because of the existence of arterial hypertension and its consequences. If this speculative conception of the

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Chapter

26

ESSENTIAL HYPERTENSION: III. CLINICAL PICTURE

ESSENTIAL hypertension appears before the physician under many guises Onsets, symptoms, and course are protean. The clinical manifesta- [illegible] cardiac failure of angina pectoris, of an organic [illegible]

[illegible]

At times, the first [illegible] or the malady may pursue a malignant course leading to death within a few months after the initial symptoms But far more often, after an insidious onset, essential hypertension runs an exquisitely chronic course [illegible] are many cases in which marked hyper- [illegible]

It is to the introduction into every-day practice of the sphygmomanometer that we owe the recognition [illegible] underlying these dissimilar clinical [illegible] as primary diseases of the particular organ from which the [illegible] symptoms emanate Only within recent decades do the textbooks of medicine contain a special section on essential hypertension. In older works, the description of the clinical phenomena of essential hypertension is to be found widely scattered under the headings of chronic interstitial nephritis, myocarditis, cerebral apoplexy, arteriosclerosis, etc.

Varieties of Symptoms in Essential Hypertension.—In the decade-long course of essential hypertension, symptoms of various origins develop. Clear differentiation of the mechanism producing the symptoms, when feasible, is very important for prognosis and treatment The principal categories are

1. *Symptoms Due to Hypertension per se* —These symptoms are alleviated when the blood pressure falls, either spontaneously or as a result of sympathectomy or other treatment. Among the truly hypertensive manifestations are some (not all) forms of headache, left ventricular hypertrophy and that component of cardiac failure which is not due to coronary arteriosclerosis Included also are the characteristic manifestations of the malignant phase of the disease, there is good evidence that hypertension produces the arteriolar necrosis which results in renal insufficiency, the retinopathy, and the cerebral edema of hypertensive encephalopathy. Both hypertension and arteriosclerosis are conjoined in the genesis of cerebral hemorrhage

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In the preceding chapter, evidence was assembled ... hypertension are on a hereditary basis. According-

prehypertensive stage is theoretical, which the physician can recognize ... many instances in which one can suspect ... that a relatively young person is in the prehypertensive stage of essential hypertension. For one thing, from at least their 'teens on, most of the individuals in question tend to have a blood pressure in the upper range of the normal. Hines[37] has shown the much greater incidence of subsequent essential hypertension in persons whose previous blood pressure was toward the ... limit of normal, while he found that those with a low blood

hypertensive, of sthenic bodily habitus and a blood pressure of about 130/90 mm. These youths are usually very strong and are often athletes whose parents remark on their great energy and freedom from fatigue. Often ophthalmoscopic examination shows thinning and unusual tortuosity of the arterial blood columns at times when the blood pressure is well within normal limits.

The question of the recognition of the prehypertensive stage by the Hines-Brown cold pressor test is discussed on page 765.

2. *The Stage of Intermittent Hypertension.*—It appears that in most, if ... of more or

hypertension. In this stage, ... normal range is punctuated by periods of hypertension. These may be frequent or far apart. Sometimes the rise in pressure seems attributable to an emotional cause, but more often such a connection is not apparent. The stage of intermittent hypertension may last for months, years or decades; little is known about this because its discovery is usually a matter of chance. During the intermittent stage the large majority of the patients are asymptomatic. However, there may be various symptoms connected with the hypertension, such as vertigo and headache or even, rarely, cerebral hemorrhage. In their study of Army officers, Levy[84] and his associ-

entered the malignant phase, in which the blood pressure remains at a constant high level, practically always, there are considerable fluctuations,

2. *Symptoms Due to Arteriosclerosis.*—Patients with essential hypertension develop, on the average, much more arteriosclerosis than do normotensives of the same age. The nature of the connection between hypertension and arteriosclerosis has not been established. However, it is important that the arteriosclerotic genesis of symptoms in patients with high blood pressure be recognized, for they are not only not necessarily ameliorated by reduction in arterial tension but may even be aggravated. A high proportion of the cardiac and cerebral manifestations is due to arteriosclerosis, and

3. *Iatrogenic Sym*

have become widesp

symptoms appear soon after the discovery of hypertension in an individual who until then had felt well. It is obviously important that symptoms of this origin be differentiated.

4. *Coincidental Symptoms.*—In a disease that lasts over decades, it is to be anticipated that symptoms of wholly independent origin will often appear. Essential hypertension is often discovered in a patient who comes to the physician for another disease. In the Outpatient Department, it has been my experience that a majority of the middle-aged women with essential hypertension have symptoms due to the climacteric, a psychoneurosis or other cause, and would usually be better off if the hypertension were unknown to them. On the other hand, in an older hypertensive the early symptoms of bronchial cancer, glaucoma or other ailments may be assumed to be due to the hypertensive disease

The Stages of Essential Hypertension.—Schematically, it is not without value to differentiate three overlapping stages of essential hypertension.

1. *The Prehypertensive Stage*—In this stage the blood pressure is within normal limits at least most of the time. However, under special circumstances in which a pressor stimulus operates, the blood pressure rises more than would be anticipated in health. The most important such circumstances are those which entail emotional stress, notably military and insurance examinations. Time and again one gets the history from a patient with essential hypertension that many years before transitory hypertension was recorded in an insurance examination, which was not again found in any of many other examinations for a number of years after. It is probably in individuals in the prehypertensive stage that hypertension accompanies the depressed phases of psychoses or periods of military exposure. I have noted evidence (family history, bodily habitus) that the exceptional instances of hypertension developing shortly after castration in the female affect individuals in the prehypertensive stage. There is similar reason to believe that in an individual in the prehypertensive stage of essential hypertension, a lesion of the kidneys or urinary tract which would not otherwise produce high blood pressure does so. Very interesting evidence in support of this conception is afforded by the observations of Hines and Lander.[56] In 284 patients with urologic disease (pyelonephritis, stones, urinary tract infections, neoplasms, etc.) whose blood pressure had been normal on their first visit to the Mayo Clinic and who were reexamined for a urologic disorder on an average of fifteen years later, they found that those whose original blood pressure was in the upper ranges of normal

. . . . ncentrate on work are often these nervous symptoms, As a result of failure to use sometimes considered as

neurotics.

In other cases, the hypertension is first revealed by the symptoms of . . . an apoplectic stroke resulting

areas of softening due to cerebral . . . palsies and other manifestations of hypertensive encephalopathy (Chapter 11) are early symptoms

In an elderly woman with essential hypertension, the symptom which first called attention to the disease was sudden amaurosis There were no . . . than the usual arteriosclerosis and the came. It was evidently a mani-

. rarely the first, manifestation of essential hypertension, hemoptysis is far less common, but I have twice seen it as an initial symptom

It is decidedly unusual that uremic manifestations usher in the clinical . . . al hypertension However, this does occur, generally in

but in other cases it results from impairment of renal . . . accompanied by polyuria

Paresthesias and pains in the extremities are not very uncommon early features, in fact, they are the less rare, the greater the care with which the history is taken They may occur in the form of intermittent claudication, particularly if there is marked arteriosclerosis. More common is a feeling of tingling, numbness or coldness in the fingers and toes Or there may be transitory "dead fingers" In other cases, the pains are of a "rheumatic" nature, occurring in the muscles of the extremities, trunk and neck

Essential hypertension of a severe variety is occasionally discovered as a result of visual disturbances and the consequent finding of hypertensive retinal changes Not very rarely, an ophthalmologist first suspects the presence of hypertension from the retinal arteries while refracting an asymptomatic patient

THE HYPERTENSION

Height of the Blood Pressure —In the large majority of patients with essential hypertension who come to the physician with subjective symptoms of the disease, the blood pressure is so definitely elevated that there can be no doubt of the existence of hypertension Usually, the systolic pressure is well over 160 mm and the diastolic over 100 mm However, one occasionally encounters cases in which the systolic pressure is about 150 mm. and the diastolic about 95 mm in a middle-aged person, so that without

which even in the severest cases at times approach the normal. The stage of continuous hypertension may last for decades.

Onset.—Nowadays essential hypertension is often discovered fortuitously in the course of a routine insurance, military, industrial or other examination. Indeed, in recent years a majority of the males—who have more routine examinations than women—with essential hypertension whom I see in private practice state that their hypertension was first noted in a routine examination. Essential hypertension is often unveiled in patients who come to the physician because of some other condition, such as the climacteric, diabetes, obesity, prostatism or emphysema.

The initial symptoms are of almost infinite variety. Often, the patient has had vague symptoms for years before he comes to the physician, and it may be impossible to determine whether these were manifestations of the hypertensive disease or due to independent conditions. Janeway[1] noted that many hypertensive patients have been subject to migraine since childhood. I have also been struck by the frequency with which hypertensive patients say they have had headaches since youth, but they are not always of migrainous character. Usually, these precursory headaches are described as different from the headaches present since hypertension appeared. Various clinicians have noted that the first manifestations of the disease often extend back to a relatively young period of life. Thus O'Hare *et al.*[2] believe that "Nature very frequently sounds a warning as early as the second decade in life of the possible development of hypertensive disease in the fourth or fifth decade" The symptoms which they found often in the early history of patients with essential hypertension were those of vasomotor and emotional instability—nose bleed, irritability, nervousness and cyanosed hands. These were present in the histories of 50 per cent of their hypertensive patients but in only 23 per cent of controls.

However, these precursory manifestations usually do not bring the individual to the physician, and even if they do, he can at most but suspect the possibility of future hypertension if there is a well-marked family history of the disease or some of the other features of the prehypertensive stage mentioned above. As has been seen above, definite hypertension appears in the vast majority of instances only beginning with the end of the fourth decade, and it is then that the individual with hypertension first comes to the physician The symptoms which bring him may be seemingly trivial or severe, recent or of long standing. The following are among the most common:

Manifestations of cardiac insufficiency are among the most frequent initial symptoms, particularly in the obese Dyspnea on exertion or following a heavy meal is perhaps the most common; or the cardiac weakness may be revealed first by palpitation, precordial oppression, swelling of the feet, nocturia, nocturnal attacks of cardiac asthma, inability to sleep on the left side, etc.

Attacks of angina pectoris not uncommonly lead to the discovery of the [illegible] infarction may be the first indication of [illegible] he previously felt well.

[illegible] sychoneurosis very frequently usher in the disease. Of these, headache is the most common. Vertigo, tinnitus,

How greatly the ordinary activities of life influence the blood pressure essential hypertension is well brought out by the observations of Smirk[6] nd his associates on the basal and what they term the casual and supplemental blood pressures (page 270). In 27 patients with essential hyper- ... averaged 196/116, the average basal

to pressor stimuli may be concerned

As a result of the strains of the day, the pressure is usually considerably higher in the evening than in the morning; this difference may reach as much as 50 mm., though generally it is less. As is the case with healthy persons, the blood pressure in essential hypertension falls during sleep. C. Mueller[7] observed that the greater the day pressure, the more pronounced the fall during sleep He described what he considered the incipient stage of essential hypertension, in which the day pressure is but ... though the night pressure is definitely above the normal

all the readings taken over a period of months may be within a range of 20 mm In such cases, rest and sedation generally have little effect on the blood pressure It is generally stated (see Ruehl[8]) that the fluctuations are

hypertension, they may even have periods of practically normal blood pressure Such cases are particularly common in climacteric women. In fact, Ayman[9] obtained one or more normal blood pressure readings in 56 per cent of his patients with essential hypertension. It is to be remarked

may be fluctuations of great amplitude even in these cases. Likewise, while the blood pressure in old hypertensive patients usually shows but slight lability, there are cases in very old persons which promptly react to bed-rest with a sharp drop in pressure

Fahrenkamp[10] has studied the fluctuations in the height of the blood pressure by constructing curves from several observations a day over a protracted period Fahrenkamp's findings will be considered in the section on Prognosis

Various events can cause a fall in the blood pressure of hypertensive individuals Most often this is due to cardiac failure, particularly when this develops acutely as a result of relatively rapidly evolving coronary

further observation or the demonstration of cardiac hypertrophy, the existence of actual hypertension is questionable. Such border-line cases are met with particularly during insurance examinations and in the examination of patients for complaints having no relation to hypertension; they will be discussed further in the section on Diagnosis.

The height of the blood pressure varies greatly in different cases. The *values encountered most frequently are around 200 mm. systolic and 110* mm. diastolic. However, the systolic pressure may reach almost 300 mm., and extremely rarely exceed it, and the diastolic even surpass 180 mm. In other cases the blood pressure remains for years around 170 mm systolic and 95 to 100 mm diastolic. In some instances the blood pressure rises rapidly; more often the rise is gradual as the patient is watched for years. On the other hand, in very many patients the height of the pressure does *not change notably from that found at the first examination, even though* it is followed for years.

Both systolic and diastolic pressures are elevated, *but not necessarily* proportionately An important factor in determining the ratio of the systolic to the diastolic pressure is the degree of arteriosclerosis of the aorta and its large tributaries. With severe arteriosclerosis, the diminished elasticity of the aorta tends to raise the systolic and lower the diastolic pressure. *In these patients* pressures such as 220/90 mm. are not uncommon. As a result of arteriosclerosis of the aorta, the ratio of the pulse *pressure to the diastolic pressure tends to be higher in older hypertensives* The effect of heart failure on the blood pressure will be discussed below.

Fluctuations in the Hypertension.—In most hypertensive patients, the height of the blood pressure is far from constant. There are great fluctuations, not only from day to day but also within a few hours The fluctuations affect particularly the systolic, but also the diastolic pressure In fact, Ayman[3] found that the percentage of fluctuation of the diastolic *pressure is as great as that of the systolic In cases in which the* lability of the blood pressure is particularly pronounced, there may be fluctuations of as much as 50 mm within a few hours In such patients, who are found particularly in the young, women with climacteric symptoms and those with evidence of emotional instability, physical and especially emotional strains are immediately documented by a rise in pressure On the other hand, mental and physical rest, particularly in bed, results in marked drop in *blood pressure, which may for a time reach normal,* though this is not common. These changes are often seen to good advantage in the hospital, where it is common to observe a blood pressure which was high on entrance drop strikingly as the patient rests in bed and becomes accustomed to his surroundings.

It appears that the taking of the *blood* pressure by the *physician almost* always acts as a pressor stimulus in hypertensive patients, who are anxious about *the result of the measurement* Ayman and Goldshine[4] found that when [illegible] home, [illegible] in the clinic. Very often the blood pressure reading obtained in the office of the consultant is higher than that of the family physician to whom the patient is accustomed.

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However, there are also many cases of essential hypertension, notably among those in the malignant phase or with heart failure, in which the blood pressure is relatively constant, there is little diurnal fluctuation and all the readings taken over a period of months may be within a range of 2

hypertension; they may even have periods of practically normal blood pressure. Such cases are particularly common in climacteric women. In fact, Ayman[9] obtained one or more normal blood pressure readings in 56 per cent of his patients with essential hypertension. It is to be remarked

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insufficiency. It is to be emphasized, however, that the development of congestive failure is by no means invariably accompanied by a fall in blood pressure (see the following section). Intercurrent febrile illness often lowers an elevated blood pressure; usually, the arterial tension returns quickly to its previous height after the fever subsides, but sometimes the pressure remains lower for a long time. Rest and other therapeutic measures may also lower the pressure, though this is often but transitory.

Blood Pressure and Other Vascular Reactions.—The reactions of the blood pressure to both pressor and depressor influences have been extensively studied in essential hypertension. Therapeutic studies will be considered in Chapter 28. The following will be restricted to the immediate effect of various agents on the blood pressure of hypertensives. O'Hare[11] long ago found that in essential hypertension, as in normals, mental and physical rest lowers the blood pressure while excitement elevates it. Nitrites cause a transitory fall in blood pressure in essential hypertension. However, O'Hare found that the fall caused by nitroglycerin may be preceded by a rise, which he attributes to excitement.

The changes in blood pressure following the injection of epinephrine appear to be much the same as in health. O'Hare observed a sharp and marked rise in pressure following the intramuscular injection of epinephrine in hypertension. Pickering and Kissin[12] found no evidence that hypertensive patients are abnormally sensitive to the intravenous injection of epinephrine. Fatherbee and Hines[13] administered by slow intravenous drip a 1 to 250,000 solution of epinephrine. They found a rise in systolic pressure of the same magnitude in hypertensive patients as in those with normal blood pressure, but noted that the diastolic pressure decreased more often in those with hypertension. Elliot and Nuzum[14] observed much the same blood pressure changes following the subcutaneous injection of epinephrine or pitressin in essential hypertension as in health

The Cold Pressor Test.—Hines and Brown[16] studied in great detail the reaction of the blood pressure when one hand is dipped in cold water They find that the blood pressure of 98 per cent of individuals with essential hypertensioı

does that of

observation

belong to hypertensive families or present evidence of arteriolar sclerosis, and whom they therefore regard as potential hypertensives, also have an abnormally great pressor response to the stimulus of cold. Hines and Brown regard an abnormally great pressor response in the *cold pressor test*, as it is known, as evidence of a hyperreactive vasomotor system Following the immersion of one hand to the wrist in ice water (4° to 5° C.) for one minute, they observed average rise of 38 mm systolic and 32 mm diastolic in individuals with outspoken hypertension as contrasted with 9 mm systolic and 7 mm. diastolic in normal controls, a rise of intermediate magnitude was observed in those whom they regarded as potential hypertensives. More recently, Hines[17] reports a mean rise in diastolic pressure of 30.9 mm. in 841 patients with essential hypertension and of 13.2 mm. in 1015 subjects with normal or usually normal blood pressure.

monium chloride and is reduced by spinal anesthesia ... extent of the arteriolar bed eliminated from vasomotor control. In a patient with transection of the spinal cord, Sullivan[20] found that immersing a hand in ice water elevated the blood pressure, while immersion of a foot did not. The rise in blood pressure in the cold pressor test is not mediated by secretion of epinephrine or arterenol, for it is not abolished by piperoxane.

When the cold pressor test was first introduced, it was hoped that it would disclose "potential" hypertensives. Support is afforded for this ... observations of Hines. He classifies as

... Hines found that ... of 58 reactors had ... of 57 hyperreactors.

Interesting as are these observations, they do not indicate that the result of the cold pressor test is more than one datum to be taken into consideration in evaluating the likelihood of future hypertension. Pickering and Kissin, Alam and Smirk,[21] and Russek and Zohman[22] all found that, while a large rise in pressure during the cold pressor test is more common in patients with essential hypertension than in normotensive controls, there are many exceptions in both groups and the excursion tends to increase with advancing age in both normotensives and hypertensives. In a seven-...

sion, Hines[17] comes to the conclusion that there is no single test of vascular

hypertensive solely on the basis of a pronounced response to the cold pressor test. The results of the test should be used as merely one line of evidence.

The Breath-Holding Test.—Ayman and Goldshine[23] test the response to vasomotor stimulation by the effect of holding the breath on the blood pressure. The patient either sits or reclines in a quiet, warm room until the blood pressure reaches a constant level. At the end of a quiet expiration, he then shuts his lips and compresses his nostrils for twenty seconds. Ayman and Goldshine find the effect of the breath-holding test—which does not involve troubling with ice water—on the blood pressure about ... the cold ...

...ther. Gubner[25] and his coworkers likewise obtained ...e cold pressor and breath-holding tests, and observed

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. . . . failure or coronary insufficiency; there were 254 ... by the ... the

... shall discuss first the ... cardiac ... In the ... ges can most often be more or less sharply differentiated.

1.
2.
3.

... in Essential Hypertension.—This is effected by

... hypertension there is hypertrophy without notable dilatation of the left ventricle, the "concentric hypertrophy" of older authors The pathological anatomist does not often see the hypertensive heart in this state of pure hypertrophy because dilatation supervenes in the vast majority of cases before death However, such hypertrophy without dilatation is occasionally encountered at necropsy in individuals who died of cerebral hemorrhage resulting from the hypertension or from conditions unrelated to the hypertension

Hypertrophy without notable dilatation of the left ventricle in essential hypertension is much more often encountered clinically A large contingent of such patients nowadays is that in which the hypertension is discovered through an insurance or health examination, though they have never had any symptoms They are seen more often in private and dispensary

...

trophy without dilating notably, there are few, if any, cardiac symptoms, unless coronary artery disease results in manifestations of angina pectoris Occasionally, the patient complains of a feeling of fulness in the cardiac ... t it is doubtful whether ... unimpaired cardiac ef- ... years or even decades During this period, the patient may be capable of very hard physical work Thus, I was acquainted with a man who had a systolic blood pressure of about 220 mm for fifteen years but nevertheless performed the hard work of a foreman in a railroad yard without difficulty during all this period

In rare instances of essential hypertension the heart copes successfully with the elevated blood pressure for a considerable time despite the absence of hypertrophy, in some of Aubertin's[31] cases of this variety the heart weighed less than 300 grams.

that the average levels reached in each of these tests in a series of patients corresponded closely to the average maximum routine measurements

Kauffmann[27] finds that in some, though not

hypertension, heat causes arteriolar constriction *instead of the normal* dilatation. In these patients the fingers became pale when immersed in hot water and the blood pressure rose in a hot room. The hypertensive patients with this paradoxical vascular reaction displayed a marked aversion to hot weather, during which they felt poorly. This behavior is the reverse of that of patients with glomerulonephritis, who generally feel better in the warmth. Westphal[28] observed that while in normals the application of the blood-pressure cuff for one minute is followed by reactive dilatation of the capillaries of the nail-fold seen through the microscope, in most patients with essential hypertension there is an inverse reaction, *i. e.*, constriction.

The vascular reactions in essential hypertension were studied plethysmographically by Lian *et al.*[15] They found that vascular reactions greater than in normals were produced by deep inspiration, the application of cold and hot water, pressure on the eyeball and carotid sinus, and the injection of epinephrine. From these findings they conclude that the sympathetic nervous system is hyperexcitable in hypertensive patients.

The subject of normal vascular reactions in essential hypertension would seem to be of importance and well worthy of further study. I am not aware that any of the observations cited in the preceding two paragraphs have been verified.

The *physical signs* of arterial hypertension have been described on page 271.

THE HEART IN ESSENTIAL HYPERTENSION

The heart of the patient with essential hypertension is confronted by two *sources of danger: increased work due to high blood pressure and impairment* of blood supply resulting from the coronary arteriosclerosis that almost inevitably develops. Despite these handicaps, there are many cases of essential hypertension in which the hypertrophied heart muscle

make their appearance sooner or later. In fact, very many individuals with essential hypertension present a clinical picture that is completely dominated by the manifestations of disease of the heart, from beginning to end they are "cardiacs." The cardiac manifestations of essential hypertension, apart from the terminal complication of uremic pericarditis in the malignant phase, consist in heart failure and angina pectoris. In an individual not aware of high blood pressure, the first intimation of disease may be a paroxysm of cardiac asthma or sudden death from myocardial infarction. Or only after decades of high blood pressure, with hard labor or repeated pregnancies, does the heart begin to weaken or anginal pains appear. In the end, a majority of patients with essential hypertension

exceptional i ... for several years and ... ginally had a very small "drop heart." One must be careful ... t as cardiac enlarge... the transverse position of the heart that often results from obesity ... fat pad near the apex. ... logicall ... left ve ... portion ... the left ventricle does not reach the borders ... to outline clearly in the oblique or

...

elliptic outline of the left ventricular border with elevation ... point above the diaphragm. The rounding is generally best visualized during inspiration, when the descent of the diaphragm exposes to view a longer sector of, or the complete, left border. But when this rounding of the ventricular segment of the left border is pronounced, there is probably already some dilatation. The pulsations as seen fluoroscopically are of smaller amplitude than in the left ventricular hypertrophy of aortic regurgitation. Evidences of elongation and dilatation of the arch of the ao... post-mortem ... fluoroscopic ... a discrepancy ...

THE ELECTROCARDIOGRAM.—While there are many patients with es... ...able severity and duration in whom the ...er the tracing reveals evi-

...

be positive when the ... patients with essentia... thectomy, Evans[35] *et al.* found 41 normal. In my office practice, the majority of patients with essential hypertension detected incidentally and without symptoms have normal electrocardiograms for their age and body type, but with symptomatology from any organ the percentage with electrocardiographic abnormalities increases. The large majority of patients ... have ab... essential ... pertrophy first of the left ventricle and then of other chambers, and to coronary arteriosclerosis.

1. *Left Axis Deviation.*—Master[34] found left axis deviation in 74 per

Evidence of Cardiac Hypertrophy.—The direct objective evidences of cardiac hypertrophy without dilatation are also not striking. It is generally agreed that hypertrophy of the myocardium does not in itself enlarge the cardiac area sufficiently to render the enlargement demonstrable as a result of displacement of the apex-beat downward or to the left. Most clinicians consider the only fairly reliable direct physical sign of hypertrophy of the left ventricle to be the heaving apex-beat, as first described by Traube.[32] By a heaving apex-beat is meant one which lifts the palpating finger with abnormally great force. It may be of small amplitude and is not to be confused with a merely prominent apex-beat of large amplitude, which is not evidence of hypertrophy but may occur in dilatation, in the overacting heart of Graves' disease or neuro-circulatory asthenia, in retraction of the left lung, and in many other conditions whether or not hypertrophy is present. But the heaving apex-beat is by no means a constant finding in cardiac hypertrophy due to arterial hypertension; at times, especially when there is pulmonary emphysema (H. A. Derow), one is unable to palpate the apex-beat at all despite extreme hypertension of long duration and no evidence of myocardial insufficiency.

Nor does percussion reveal definite enlargement of the heart to either left or right. Increase in retromanubrial dulness may result from dilatation and elongation of the aorta with consequent wider approximation of the vessel to the anterior chest wall.

The first apical sound of the hypertrophic heart is often, though not [illegible]

tion and other changes in the aortic second sound have already been described (page 272). Systolic murmurs at the apex and base are not uncommon, sometimes, they arise from atherosclerotic changes in the valves and aorta. Far less often, the latter produce a regurgitant murmur. A diastolic murmur akin to that of organic aortic insufficiency was long ago observed in hypertensive patients by Gibson[33] and Kahler;[34] in 3 of the latter's cases, necropsy revealed no aortic insufficiency, so the murmur must have been "functional" Such functional diastolic murmurs are, however, apparently rare in hypertension, though perhaps not as rare as is generally thought I have heard evanescent diastolic murmurs in the aortic area in several cases of essential hypertension with uremia and in at least 2 of these necropsy disclosed no organic leak The pathogenesis of these diastolic murmurs is not obvious; they are perhaps due to a combination of dilatation of the terminal portion of the outflow tract of the left ventricle and stretching of the aortic ring by the high aortic pressure.

X-ray Findings.—The radiographic examination most often does not furnish unequivocal evidence of left ventricular hypertrophy as long as significant dilatation is absent—so-called concentric hypertrophy While the teleoroentgenogram or orthodiagram generally shows that the left transverse diameter is above the average, it does not exceed the upper limit of normal in the absence of dilatation It is to be emphasized that careful *x-ray examination of the heart may reveal no enlargement or alteration in contour despite hypertension of even five years known duration.* There are

3. *Changes in the RS-T Segment and T Wave.*—Master observed that the ... inverted in the *first lead and sometimes also in the second* ... Whitten[4] showed

used the term left ventricular strain) the T wave ... perhaps also the second lead, while in right ventricular strain ... The full-blown electro- ... n essential hypertension includes a depressed RS-T junction, a depressed RS-T segment which is ... T wave in the first and perhaps also the

The usually depressed RS-T junction in the ... differentiation from T-wave inversion due to

leads, Sokolow and Lyon elicited abnormal RS-T or T changes in ... 147 patients with left ventricular hypertrophy (90 per cent hypertensive). As Master, Wilson *et al*, and these investigators point out, the segmental and T wave changes in hypertension are greatly influenced by the position ... In the large majority of hypertensives the heart is horizontal

T wave in the sec- ... vertical heart to be

460 normals with left axis deviation, Gubner and Ungerleider regard an RS-T depression of as little as 0.5 mm in the first lead in a hypertensive

habitus and frequently obese, with a resultant transverse position of the heart. The importance of body build for the production of left axis deviation is shown by Gubner and Ungerleider's[37] finding that its incidence varies *pari passu* with the percentage variation of the body weight from the average. In stocky or obese individuals, left axis deviation is the rule even though the left ventricle is not hypertrophied and the blood pressure normal, especially in the elderly. Left axis deviation is often absent, or the electrical axis even rotated to the right, in slender individuals with essential hypertension despite marked left ventricular enlargement. In the later stages of cardiac insufficiency in essential hypertension, enlargement of the right side of the heart may cause the disappearance of left axis deviation.

2. *High Voltage and Other Changes in the QRS Complex.*—High amplitude of the QRS is a common and important, though not constant, manifestation of left ventricular hypertrophy in essential hypertension. It may antedate all other changes in the electrocardiogram. Gubner and Ungerleider found that whereas the sum of R_1 and S_3 is less than 2.2 millivolts in 95 per cent of normals with left axis deviation, this voltage is exceeded in 67 per cent of individuals with left ventricular hypertrophy. High voltage is indicative of left ventricular hypertrophy only in association with left axis deviation, for in the absence of the latter it is often found normally, especially in the slender. High voltage of the QRS is often observed during the stage of concentric hypertrophy and is probably a manifestation of the increased mass of the myocardium of the left ventricle (*cf.* Wilson[38] *et al.* and Lipman and Massie[39] for the factors possibly involved) However, Robb and Robb[40] found that increased voltage occurs in rabbits as a result of acute left ventricular strain before hypertrophy could develop.

In the precordial leads, the most common finding in the left ventricular hypertrophy of essential hypertension is a low or absent R and deep S in V_1 and V_2 and a tall R in V_5 and V_6. Sokolow and Lyon[41] found that the sum of the total left ventricular potentials (S in V_1 plus R in V_5 or V_6) rarely exceeded 30 mm. in health but was greater than this in 49 per cent of patients with left ventricular hypertrophy.

The duration of QRS may be increased to 0.12 seconds in left ventricular hypertrophy in the absence of the electrocardiographic pattern of bundle branch block. Sokolow and Lyon found a QRS of 0.11 or 0.12 second in 18 of 147 patients with left ventricular hypertrophy Wilson and his associates pointed out that in ventricular hypertrophy the time required for passage of the impulse to the epicardium may be prolonged. Sokolow and Lyon found this ventricular activation time, as measured from the onset of QRS to the peak of R, was prolonged above the normal in V_5 or V_6 in 58 per cent of their patients with left ventricular hypertrophy. Kossman[42] points out that if the peak of the R wave is more than 0.03 later than the onset of QRS in V_5 than in V_1, it suggests preponderant hypertrophy of the left ventricle.

Q waves of modest size in relation to the R waves are common in left ventricular hypertrophy in the leads toward which the left ventricular potentials are directed. Wilson *et al.* observed them in V_5 and V_6 in more than half and Sokolow and Lyons in about one-third of their cases. It should be remembered that Q waves may be found normally in these leads.

THE BALLISTOCARDIOGRAM.—Chesky[58] *et al.* studied the ballistocardiogram in 50 hypertensive patients Abnormal tracings were obtained in 38, including many with normal electrocardiograms. As yet, ballistocardiographic changes specifically correlated with hypertension have not been differentiated

CIRCULATORY MEASUREMENTS in essential hypertension are discussed i [illegible] cardiac [illegible] Some- [illegible] nifesta- [illegible] tions though in such cases examination usually indicates [illegible] asympto- [illegible] ther patients heart [illegible] known high blood [illegible] ompensation, for it [illegible] much remains to be learned [illegible] heart failed.

One factor that is probably of primary significance in the pathogenesis of most instances of heart failure in hypertension is *progressive insufficiency of the blood supply to the left ventricle.* This chamber performs increased work to cope with the increased peripheral resistance and hypertrophies in consequence The bigger muscle mass performing the greater work doubtless requires a more ample blood supply than does a left ventricle of normal size carrying on the usual work This is all the more likely in the light of [illegible] hyp [illegible] the [illegible] he [illegible] cardiac compensation in hypertension itself plays a fundamental rôle in the ultimate failure of the heart For the increased muscle mass calls for corresponding augmentation of blood supply and even moderate sclerotic [illegible]

demonstrated by the important investigations of Wearn He found that in both the normal adult and the hypertrophied heart there is approximately one capillary per muscle fiber But since each muscle fiber in the hypertrophied heart is thicker, the "concentration" of capillaries falls. Wearn found that for each cubic centimeter of myocardium the normal adult heart contains 1,184 square centimeters of capillary surface area, while

nation may reveal no disease of the coronary arteries or histological changes other than hypertrophy. Whatever the mechanism of the RS-T and T changes, it is reversible, for after sympathectomy the RS-T segment may rise and the inverted T wave again becomes upright. Yet to be explained is that this may occur even though the blood pressure changes little. Normalization of the RS-T and T changes of hypertension has also been observed as a result of sodium restriction (Bryant and Blecha[44]) or the administration of large doses of potassium (Sharpey-Schafer,[45] Bryant[46]). Perhaps the most probable explanation of the electrocardiographic picture in question is that it is due to relative ischemia of the left ventricle, which in many instances results more from increase in muscle mass than decrease in coronary flow. This explanation equates the pathogenetic mechanism of the electrocardiographic changes with that which probably ultimately causes the failure of the hypertrophied ventricle (page 773). Gubner and Ungerleider point out that the ischemia of coronary insufficiency is most apt to affect the subendocardial region of the left ventricle, where intramyocardial pressure is highest, and the RS-T and T changes of ventricular hypertrophy have many features in common with those resulting from coronary insufficiency. For these reasons they believe that the RS-T and T changes in left ventricular hypertrophy may result from relative ischemia of the subendocardial portions of the left ventricle. Boyer and Hewitt[47] regard their vector studies as opposed to the ischemia theory. They interpret their analysis of the vectors as indicating that the inversion of the T wave in hypertension is secondary to increase in the area beneath the QRS as projected on the frontal plane, which they regard as the primary change, perhaps augmented by decrease in the magnitude of the ventricular gradient On the basis of these observations, Boyer and Hewitt question the theory that the T wave inversion of left ventricular hypertrophy is due to ischemia, and believe that both the QRS and the T changes may be due to changes in the rotation and position of the heart. To the writer, however, the predominant weight of evidence seems highly suggestive that the RS-T and T changes of left ventricular hypertrophy are due to a metabolic alteration in the heart muscle of ischemic origin; this conception accords well with the fact that ultimately electrocardiographic changes—notably incomplete bundle branch or arborization block—suggestive of damage to the subendocardial myocardium develop in a high proportion of the cases and anatomical examination reveals patchy fibrosis

4 *Electrocardiographic Changes Due to Coronary Arteriosclerosis and Thrombosis* —At any stage of essential hypertension, electrocardiographic changes due to coronary artery disease may develop. In evaluating the electrocardiogram of a hypertensive patient, it is always necessary, though often difficult, to differentiate between the changes due to ventricular hypertrophy or shift in the position of the heart and those resulting from coronary narrowing.

For discussions of the
hypertrophied heart, the
and Scherlis[48] and Estes a... [illegible]
graphic interpretation promises to add to understanding of the hypertensive heart.

or other symptoms of heart failure to which little attention has been paid. Among the circumstances which may thus bring hitherto disregarded cardiac weakness to the attention of patients are emotional upsets, lifting

a patient who previously

acute precipitants merely bring to the surface symptomatically latent heart failure by increasing the work of a left ventricle the functional reserve of which had already been narrowed.

3. *Infections.*—On rare occasions, an upper respiratory, pulmonary or other infection in a previously well compensated individual with hypertension is followed by heart failure. This may occur during the febrile period, or become manifest only after the patient leaves bed. In my experience, the number of instances of heart failure in hypertension which have been definitely precipitated by an intercurrent infection has been very small. Even before the days of antibiotics, hypertensives usually passed through severe infections, such as lobar pneumonia or typhoid fever, without developing heart failure; peripheral circulatory failure was a greater risk Bronchopneumonia is much more often a *consequence* of left heart failure, usually through the intermediacy of pulmonary infarction, than it is a *cause* of cardiac insufficiency.

4 *Superelevation of the Blood Pressure* —There is no close correlation between the height of the blood pressure in essential hypertension and the liability to heart failure. In relatively young individuals in whom essential hypertension enters the malignant phase, the arterial pressure, especially the diastolic, is usually very high, and yet they almost always succumb to renal insufficiency with the cardiac manifestations in the background of the clinical picture until the last days. Especially in middle-aged women just past the menopause it is not uncommon to observe systolic pressure over 250 and diastolic pressure over 130 mm. for several years with little cardiac enlargement and no evidence of cardiac insufficiency except on

in exceptional cases with widely fluctuating blood pressure, an abrupt and marked rise of blood pressure seems on rare occasions to precipitate acute left ventricular failure. This sequence is seen in classical form in true paroxysmal hypertension due to pheochromocytoma That most instances of acute left ventricular failure with pulmonary

bably a more sig-
pressure; indeed,
systolic pressure,
diastolic pressure most often is either unchanged or falls

the hypertrophied heart averages only 623 square centimeters. It is thus evident that gaseous diffusion and other metabolic exchanges are handicapped in the hypertrophied heart because they must take place over a longer distance. Further support for the conception that the blood supply to the hypertensive heart does not keep pace with the hypertrophy is afforded by the finding of Gross and Spark[52] that the average number of arterioles per low power field diminishes in inverse proportion to the weight of the heart.

Progressive insufficiency of the metabolic exchanges between blood and heart muscle due to the enlargement of the muscle fibers may alone cause heart failure in some hypertensive patients. But in other cases, the actual appearance of clinical symptoms of heart failure is precipitated by various factors which accentuate the disproportion between the functional capacity of the left ventricle and the demands made on it. Among these are the following:

1. *Clinically Manifest Coronary Arteriosclerosis.*—In the foregoing, we have seen that coronary arteriosclerosis is probably one of the underlying pathogenetic factors in most instances of heart failure in essential hypertension. Sometimes, however, the coronary sclerosis produces neither clinical symptoms nor electrocardiographic changes. And exceptionally, even at necropsy, the sclerosis may compromise the lumens of the coronary arteries so little that one would attribute slight significance to it, were there not the greatly hypertrophied left ventricle with its need of an abnormally large blood supply. But in other cases, the coronary arteriosclerosis is so severe that it is obviously the principal and immediate cause of the heart failure. The latter may be initiated suddenly by major coronary thrombosis, or by a change in rhythm. Or the coronary artery disease may be revealed by either anginal pains or electrocardiographic evidences of myocardial damage, which, in long-standing hypertension, one is generally safe in attributing to narrowing of the coronary arteries. Averbuck[193] found that severe coronary arteriosclerosis was present in necropsy in 85 per cent of patients with essential hypertension who had heart failure, but in only 10 per cent of hypertensive individuals without cardiac insufficiency. In a large majority of the necropsies that I have seen on hypertensive patients succumbing to heart failure, actual coronary occlusions or extreme narrowing of coronary branches with focal scarring of the myocardium have been present Such a manifestly coronary origin of heart failure in hypertension appears to be more common in the male. In individuals with both hypertension and diabetes, coronary arteriosclerosis is generally very severe and is most often the manifest cause of heart failure. Similar preponderance of the coronary element in the causation of heart failure is more common in the very old than in the relatively young individual with hypertension. In the heart failure that is not uncommon, in addition to renal insufficiency, in the terminal stages of the malignant phase of essential hypertension, the coronary element is usually absent or slight.

2. *Overexertion.*—Not uncommonly, patients with hypertension attribute their symptoms of heart failure to some physical or emotional stress Most often, careful interrogation elicits antecedent dyspnea on exertion

...ded heart failure may produce "functional" emphysema. The engorgement of the lungs erects the vessels and interferes with expiratory collapse, and thus tends to maintain the lungs in an average position closer to that of inspiration than in health Emphysema may be either cause or con-

considerable period before. If the dyspnea is ... especially careful search should be made for coronary insufficiency or myocardial infarction Nocturnal cough regarded as "bronchitis," palpitation and a feeling of weight in the region of the heart are other frequent early complaints. Obese persons often delay visiting their physician because they attribute these symptoms to adiposity. Abdominal pain, distention and flatulence, perhaps due to congestion of the liver and other abdominal viscera, are occasional early manifestations of weakening of the hypertensive heart; the patient may think his symptoms are due to primary gastric or intestinal trouble and often attempts to treat them with cathartics or antacids Nocturia or inability to sleep on the left side are common complaints as the heart becomes inadequate; older men often blame the former on prostatism The early symptoms of heart failure in essential hypertension are often commingled with anginal manifestations of coronary insufficiency, and the physician may be hard put to differentiate them.

The Stage of Left Ventricular Failure.—Heart failure in essential hypertension most often sets in with symptoms due to engorgement of the pulmonary circuit without accompanying evidences of stasis in the tributaries

... clinical picture, the main features of which, in a typical case, are as follows

a Dyspnea on exertion and, what is more characteristic when present, attacks of cardiac asthma The dyspnea is often accompanied by orthopnea

b Absence of peripheral venous stasis and its consequences.

..., though this may be

e Fall in blood pressure, but this is far from constant (see page 788).

5. *Obesity.*—Individuals with essential hypertension are often obese, and when the adiposity is marked it may play a rôle in the production of cardiac insufficiency. The excessive body weight, of course, increases the work of the heart, especially during physical exertion. Also, the upward displacement of the diaphragm due to enlargement of the omental and other fat depots in the abdomen in most obese persons places the heart in a more transverse position, in which it may work at a mechanical disadvantage. Furthermore, in extremely obese individuals there may be extensive deposition of fat under the epicardium with infiltration between the myocardial fibers down to the endocardium (so-called *lipomatosis cordis*). Not uncommonly, symptoms of heart failure in obese persons with high blood pressure are alleviated when body weight is reduced

6. *Complicating Valvular Lesions.*—Arteriosclerotic changes in the mitral and aortic valves are common in long-standing essential hypertension. Usually, they are merely post-mortem discoveries, though they may produce systolic murmurs Less often arteriosclerotic changes produce [illegible]

[illegible] Essential hypertension develops frequently in middle-aged women with rheumatic mitral stenosis (page 791). The combination of arterial hypertension and mitral stenosis does not seem especially unfavorable as regards the production of heart failure. I have seen many cases in which they have co-existed for years without heart failure. Indeed, it seems plausible that the narrowing of the mitral ostium tends to spare the left ventricle. But patients with both mitral stenosis and essential hypertension are much more apt to develop auricular fibrillation than those with only high blood [illegible] ular fibrillation in an [illegible] occult mitral stenosis should be borne in mind, even though characteristic murmurs are not audible during the period of rapid heart action.

The association of essential hypertension with aortic regurgitation of rheumatic or syphilitic etiology is not as common as with mitral stenosis (except in population groups with a high incidence of syphilis), but is not rare. Of course the purely systolic hypertension of aortic regurgitation must [illegible]. While some of the cases [illegible] syphilis are especially apt to [illegible], sudden death is common, [illegible] ry ostia

7. *Emphysema.*—This is a frequent complication in older hypertensives and often seems to play a part in the production of heart failure The clinical picture in the late phases may be predominantly that of cor pulmonale. This occurs in that stage in which, as a result of weakening of the left heart, the pressures in the pulmonary circuit have risen and the right ventricle has hypertrophied; the development of emphysema naturally throws a further strain on it. In fact, it is not uncommon in patients with essential hypertension and emphysema that the latter seems to be the more important factor in causing the cardiac breakdown; in two such cases, the right ventricle was found at necropsy to be considerably more hypertrophied and dilated than the left. It should be borne in mind that left-

ccurs an ... of pulmonary edema ...

transudation into the alveoli to a relative predominance ...
tricle over the left with consequent increase in pressure in the pulmonary

in blood flow to the brain, the investigations of Harrison[..] have shown that left ventricular failure produces cardiac asthma through the intermediacy of pulmonary engorgement and consequent decrease in vital capacity As Harrison's studies show, the actual paroxysm is precipitated by intensification of the pulmonary engorgement, which may become so marked as to produce pulmonary edema. In the production of the pulmonary engorgement, combination of the recumbent position and sleep appear to be of fundamental importance The recumbent position produces a shift of blood from the abdomen and lower extremities to the lung; with a weakened left ventricle the result is pulmonary engorgement and consequent decrease in vital capacity And the diminished sensitivity of the nervous system during sleep presumably allows this engorgement to attain a higher degree than would otherwise be the case Among the other factors which may participate in the nocturnal intensification of pulmonary ... of manifest or occult ... in ... of ... the erect to the recumbent posture—is probably the most important factor in many attacks of cardiac asthma This conception is supported by the observations of Perera and Berliner,[62] who found in patients with nocturnal cardiac asthma that the plasma protein concentration is lowered after several hours in bed and then again rises ten or fifteen minutes after the onset of the paroxysm, when the patient has sat up and gasped for some time—defensive acts which tend to terminate the attack. It is probably through lessening the volume of extracellular fluid and thus decreasing the amount resorbed at night that sodium restriction and mercurial diuresis often prevents the attacks

Orthopnea is often a striking characteristic of the breathlessness of left-sided heart failure. This is not surprising, for there is good evidence to show that orthopnea is a manifestation of pulmonary engorgement.

A paroxysm of cardiac asthma may occur at any time of the night, but is most common in the first hours of sleep. The patient may have felt well before retiring or he may have been dyspneic. He awakens sud-

1. Dyspnea on Exertion and Cardiac Asthma. D-
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tensive heart to t [illegible]
such task as clim[illegible] [illegible] walking against the wind, or after a heavy meal. The dyspnea may be very intense [illegible] e or almost [illegible] nea is com- [illegible] Patients, [illegible] subjective [illegible] is atypical it may be dif- [illegible] to decide whether the thoracic, cervical or epigastric discomfort induced by exertion is dyspnea or angina pectoris, *i. e.*, whether the symptom is respiratory embarrassment due to weakness of the left ventricle or the pain of myocardial ischemia produced by the coronary arteriosclerosis so common in essential hypertension. The differentiation is an important one, especially for rational therapy, but unfortunately can not invariably be made with certainty. Doubtless, dyspnea and angina pectoris are often combined to form a complex sensation.

Cardiac Asthma.—The dyspnea of effort may be accompanied by attacks of cardiac asthma. Or, what is not rare, cardiac asthma is the only symptom pointing to insufficiency of the left ventricle, the dyspnea on exertion being so slight that a patient leading a sedentary life does not complain of it, and its existence i[illegible] oning, if at all. Rarely, a paroxysm of [illegible] which leads the patient with essential hypertension to seek medical aid. Failure to measure the blood pressure has resulted in such patients being treated for true bronchial asthma.

The term cardiac asthma is applied to paroxysms of dyspnea occurring when the patient is at rest, as a rule awakening him from sleep, and often accompanied by demonstrable acute edema of the lungs. In 94 per cent of Pratt's[54] cases, the initial seizure occurred while the patient was quiet in bed. Cardiac asthma is a symptom of left ventricular failure. This is most often due to hypertension. Pratt found that in 18 of 30 patients with cardiac asthma the systolic pressure was abnormally high, while in 17 of 23 cases in which he determined the diastolic pressure, this was above 100 mm. He considers it probable that in some of the patients in whom the blood pressure was within normal limits, it had been previously elevated. However, hypertension is not the only cause of cardiac asthma. Typical attacks of cardiac asthma are not uncommon in syphilitic aortitis (9 of Longcope's[55] 63 cases) and coronary artery disease, in the former presumably most often when the mouths of the coronary arteries are narrowed. They also occur in the left ventricular failure of rheumatic aortic insufficiency, particularly when there is marked systolic hypertension. Cardiac asthma is extremely rare in pure mitral disease. It seems that in most of the cases of essential hypertension in which cardiac asthma occurs, there is also well-marked coronary artery disease. Hypertensive patients who have never before had cardiac asthma not uncommonly first develop such attacks after renal insufficiency has set in.

The basis on which cardiac asthma occurs is insufficiency of the left ventricle. The contractile power of the right ventricle is either unim-

always, leads to the production of pulmonary edema. At least in some attacks of cardiac asthma in which neither the expectoration nor the physician's examination afford evidence of pulmonary edema, the latter may be disclosed by transitory cloudiness of the lung field in the x-ray picture. In fact, the frequent occurrence of pulmonary edema in the cardiac asthma

tricle over the left with consequent increase in pressure in the pulmonary capillaries

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1. Dyspnea on Exertion and Cardiac Asthma.—Dyspnea on exertio is the complaint which most often brings the patient with a failing hype tensive heart to the doctor. It may be noticed only when performing som such task as climbing stairs or walking against the wind, or after a heav meal. The dyspnea may be very intense despite the complete or almos complete absence of signs of peripheral venous stasis. Orthopnea is com mon in left ventricular failure and may be the initial complaint. Patient even when physicians, use many analogies to describe the purely subjectiv sensation of dyspnea, and when the description is atypical it may be dif ficult to decide whether the thoracic, cervical or epigastric discomfor induced by exertion is dyspnea or angina pectoris, *i. e.*, whether the symp tom is respiratory embarrassment due to weakness of the left ventricle o the pain of myocardial ischemia produced by the coronary arterioscleros so common in essential hypertension.The differentiation is an importan one, especially for rational therapy, but unfortunately can not invariabl be made with certainty. Doubtless, dyspnea and angina pectoris are ofte combined to form a complex sensation.

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and edema of the lungs, the peripheral ... pensating for the weakening of the left ventricle (see page 789). In other cases, however, the reverse is true and the blood pressure drops; this occurs especially if the attack is due to myocardial infarction.

An attack of cardiac asthma may last from a few minutes to several hours; often, the paroxysm is over before the doctor arrives. Pratt found the average duration in 26 cases to be one hour. After the attack, the ... More often, however, particularly ... the breathing becomes rather easy ... may feel comparatively well the next

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paratively infrequent ... of acute left ventricular insufficiency, the patient dies before the physician sees him in the attack. I have seen many fatal attacks of cardiac asthma.

There may be only a single attack of cardiac asthma or a few seizures at ... in exceptional cases the paroxysms recur with great

restriction and mercurial diuretics. With the advent of ... peripheral venous stasis the attacks usually become less frequent or disappear, presumably because of diminution in the predominance of the right ventricle.

Varieties of Dyspnea in Hypertensive Patients.—It is to be remembered that various pathogenetically distinct varieties of dyspnea are observed in hypertensive patients, among which are:

a. Dyspnea on effort, due to left ventricular failure.

d. Paroxysmal dyspnea which is apparently due to diminished blood supply to the respiratory center, either as a result of cerebral arteriosclerosis or of cerebral vasoconstriction in hypertensive encephalopathy. In this form there is no acidosis and there may even be well-marked alkalosis as a result ... ib and Meier, see

f. Emphysema often contributes to the production of dyspnea in patients with essential hypertension.

2. ABSENCE OF PERIPHERAL VENOUS STASIS.—Evidences of venous stasis are absent in typical instances of isolated failure of the left ventricle, the hypertrophy of the right ventricle compensating for the weakness of the left heart. The venous pressure is normal. In other cases, however, slight insufficiency of the right ventricle is demonstrated by a little enlargement of the liver or puffiness of the ankles which clears up after a night's rest. But these symptoms of weakness of the right ventricle are over-

denly with an agonizing sense of suffocation and great difficulty in breathing. In mild attacks, this quickly passes off, he draws a few deep breaths, perhaps expectorates a little viscid sputum, and drops off to sleep again. As mild "equivalents" of cardiac asthma, Pratt describes paroxysmal nocturnal cough and paroxysmal nocturnal anxiety. Such equivalents can, however, be recognized only if the patient has typical seizures of cardiac asthma on other nights.

The more severe attacks are terrifying in the extreme, both to patient and onlooker. The dyspnea is of the utmost severity. The patient sits up in bed or at the side of the bed; he may go to a chair or to the window. The face has an agonized expression; at first there is an ashen pallor which changes to a dusky cyanosis as the paroxysm persists. The head is bent forward, the hands grasp the sides of the bed and every muscle is brought into play in an effort to overcome the terrible sensation of impending suffocation. Often, the sufferer either cannot or is afraid to interrupt breathing long enough to say a word, or he may gasp for water between breaths. The breathing is noisy and wheezing or râles may be audible to bystanders. Often the patient himself hears wheezing or a "cooking" sound, these may be audible to him before he is aware of the shortness of breath. Often it is obvious that the dyspnea is expiratory, as in bronchial asthma. Short coughs may interrupt the breathing. If the pulmonary edema becomes great, there is expectoration of the characteristic pink, frothy sputum. Or bloody mucus may be brought up, which sometimes signals the termination of the attack.

Pain is not characteristic of cardiac asthma; after the paroxysm the patient most often says that his agony was entirely due to the sense of suffocation. Of course, if the sudden failure of the left ventricle resulted from coronary insufficiency, there may be an anginal attack combined with the cardiac asthma—the *angine de décubitus* of Vaquez[63] An attack of cardiac asthma may herald a myocardial infarction even though there is little or no pain. Especially older patients should be studied electrocardiographically after an attack of cardiac asthma

The most striking finding during a severe attack of cardiac asthma is the presence of the moist râles of pulmonary edema throughout both lungs. Even in mild attacks moist râles may be present at both bases There may also be wheezing akin to that of bronchial asthma. The heart sounds are often difficult to hear because of the noisy breathing, gallop rhythm is usually present, even though it was absent before the attack. It would seem probable that there is acute dilatation of the left ventricle during the seizure, though I am not aware that any one has actually demonstrated this. The pulse is rapid, usually small, and sometimes irregular

Some observations by Amblard[33] would seem to indicate that at the very beginning of the attack the blood pressure, particularly the systolic, falls, evidently because of failure of the left ventricle. But at the height of the attack, Pratt, Amblard, and others have found that the blood pressure sometimes rises notably. I have often seen both the systolic and diastolic pressures rise strikingly during a paroxysm of cardiac asthma, to fall to its previous level after morphine has taken effect. Presumably, the rise in

blood pressure is due to the asphyxia resulting from the circulatory failure and edema of the lungs, the peripheral vasoconstriction more than compensating for the weakening of the left ventricle (see page 780). In other cases, however, the reverse is true and the blood pressure drops; this occurs especially if the attack is due to myocardial infarction.

An attack of cardiac asthma may last from a few minutes to several hours, often, the paroxysm is over before the doctor arrives. Pratt found the average duration in 26 cases to be one hour. After the attack, the

More often, however, particularly the breathing becomes rather easy may feel comparatively well the next

morning.

Despite the terrifying aspect of a severe attack of cardiac asthma, death during the paroxysm is considered by Pratt and most others to be comparatively infrequent. It may well be, however, that in the severest forms of acute left ventricular insufficiency, the patient dies before the physician sees him in the attack I have seen many fatal attacks of cardiac asthma.

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ventricle

b Cardiac asthma, which also arises on the basis of weakness of the left ventricle but occurs when the individual is at rest

c Uremic dyspnea, which is a true acidotic dyspnea and accompanies lowering of the bicarbonate of the blood

d Paroxysmal dyspnea which is apparently due to diminished blood supply to the respiratory center, either as a result of cerebral arteriosclerosis or of cerebral vasoconstriction in hypertensive encephalopathy. In this form there is no acidosis and there may even be well-marked alkalosis as a result

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2 Absence of Peripheral Venous Stasis — Evidences of venous stasis are absent in typical instances of isolated failure of the left ventricle,

rest But these symptoms of weakness of the right ventricle are over-

shadowed by the manifestations of left ventricular failure. Such a stage may persist for many years or be completely relieved by therapy. Ultimately, if the patient does not succumb during the stage of left ventricular failure, the right heart also gives way, signs of venous stasis appear, and the isolated insufficiency of the left ventricle is replaced by the typical picture of insufficiency of the whole heart.

3. Dilatation of the Left Ventricle.—This occurs as the myocardium weakens as a result of the factors discussed above (page 773). While enlargement was but slight during the stage of "concentric" hypertrophy, the addition of dilatation is marked by demonstrable increase in the size of the left ventricle. The apex-beat is found displaced to the left and downward and with marked dilatation is in the sixth or seventh interspace and outside the mid-clavicular line, sometimes reaching past the anterior axillary line. However, in the initial stages of dilatation of the left ventricle the apex-beat may be displaced downward before it is demonstrably out to the left. The apex-beat is less forceful than before the onset of dilatation, but is usually of greater amplitude and more diffuse. Only with pronounced dilatation is the downward and outward enlargement of the left ventricle demonstrable by percussion.

On auscultation, the heart-rate is generally found to be accelerated. However, there are cases of hypertension with symptoms of left ventricular failure in which the heart-rate is surprisingly slow despite the absence of block. Extrasystoles are occasionally present, but auricular fibrillation is rare during the stage of isolated insufficiency of the left ventricle.

Gallop rhythm is the only important auscultatory manifestation of left ventricular failure in hypertension. When present—and it should not be confused with splitting of either the first or the second heart sounds—gallop rhythm furnishes unequivocal evidence of left ventricular failure. It may be heard in patients without subjective complaints. However, gallop rhythm is not present in by any means all hypertensives with left ventricular failure, and may be absent in cases of even maximal severity. Gallop rhythm which is not audible at rest may be easily heard in the first beats after mild exercise; I have found this a valuable maneuver which sometimes furnishes the only evidence that the left ventricle of a hypertensive patient is functionally impaired.

The dilatation of the left ventricle is generally accompanied by the appearance of the systolic murmur of relative mitral insufficiency. Fahr[64] found an apical systolic murmur in 80 per cent of hypertensive patients with cardiac insufficiency. Often very characteristic is accentuation of the pulmonic second sound as the left ventricle weakens with resultant increase in tension in the pulmonary circuit. Simultaneously, the aortic second sound may weaken.

X-Ray Findings.—It was seen above that concentric hypertrophy of the left ventricle causes either no
of the ventricular segment of the
does reveal the advent of any considerable dilatation.
evidence of dilatation consists in pronounced rounding of the left lower border with *elongation*. At this stage the broadening is not considerable enough to be unequivocally demonstrable by increase in the transverse

diameter With well-marked dilatation the chamber appears like an obliquely placed egg, the long diameter extending from the midline downward and outward. The elongated ventricle may reach so far into the diaphragmatic shadow that the egg-like shape and rounding of the left border are apparent only during deep inspiration. Examination with the left shoulder to the screen reveals a backward bulging of the posterior surface of the left ventricle into the retrocardiac space so that it reaches or passes well over the vertebral shadow. This posterior enlargement may be demonstrable with but moderate dilatation by the finding that when the patient is slowly rotated toward the left oblique and then the lateral position, the left ventricle does not "clear" the spine until the normal angle of rotation of 55 degrees has been exceeded (*cf.* Schwedel,[a] who gives the quantitative shortcomings of this measurement) Dilatation, like hypertrophy, of the left ventricle in hypertension involves first the outflow and then the inflow tract According to Schwedel, the radiologic signs of enlargement of the outflow tract are elongation downward and rounding of the left ventricular contour. He enumerates the radiologic evidences of enlargement of the inflow tract as increase in the length of the left ventricular segment, rounding of the left upper contour and a bulge posteriorly, and displacement of the interventricular groove downward and forward. Reliably to elicit these changes requires an observer of great experience in the radiology of the heart. For an authoritative account of the subject, the reader is referred to the monograph of Schwedel.

The pulsus alternans may accompany isolated insufficiency of the left ventricle, t

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inflated above the systaking a blood-pressure out while the observer in which only half the beats come through Gallavardin suggests another maneuver, not as

and mercurials in the treatment of heart failure has become general, alternation of the pulse has become a rarity.

4 Evidences of Stasis in the Lesser Circulation.—Apart from acute episodes of pulmonary edema, there are evidences of stasis in the lesser circulation in most instances of insufficiency of the left ventricle. The dilatation of the left ventricle is sooner or later followed by incomplete

shadowed by the manifestations of left ventricular failure. Such a stage may ... lieved by therapy. Ultimatel ... the stage of left ventricular failure, the right heart also gives way, signs of venous stasis appear, and the isolated insufficiency of the left ventricle is replaced by the typical picture of insufficiency of the whole heart.

3. Dilatation of the Left Ventricle.—This occurs as the myocardium weakens as a result of the factors discussed above (page 773). While enlargement was but slight during the stage of "concentric" hypertrophy, the addition of dilatation is marked by demonstrable increase in the size of the left ventricle. The apex-beat is found displaced to the left and downward and with marked dilatation is in the sixth or seventh interspace and outside the mid-clavicular line, sometimes reaching past the anterior axillary line. However, in the initial stages of dilatation of the left ventricle the apex-beat may be displaced downward before it is demonstrably out to the left. The apex-beat is less forceful than before the onset of dilatation, but is usually of greater amplitude and more diffuse. Only with pronounced dilatation is the downward and outward enlargement of the left ventricle demonstrable by percussion.

On auscultation, the heart-rate is generally found to be accelerated. However, there are cases of hypertension with symptoms of left ventricular failure in which the heart-rate is surprisingly slow despite the absence of block. Extrasystoles are occasionally present, but auricular fibrillation is rare during the stage of isolated insufficiency of the left ventricle.

Gallop rhythm is the only important auscultatory manifestation of left ventricular failure in hypertension When present—and it should not be confused with splitting of either the first or the second heart sounds—gallop rhythm furnishes unequivocal evidence of left ventricular failure It may be heard in patients without subjective complaints. However, gallop rhythm is not present in by any means all hypertensives with left ventricular failure, and may be absent in cases of even maximal severity. Gallop rhythm which is not audible at rest may be easily heard in the first beats after mild exercise; I have found this a valuable maneuver which sometimes furnishes the only evidence that the left ventricle of a hypertensive patient is functionally impaired.

The dilatation of the left ventricle is generally accompanied by the appearance of the systolic murmur of relative mitral insufficiency. Fahr[64] found an apical systolic murmur in 80 per cent of hypertensive patients with cardiac insufficiency. Often very characteristic is accentuation of the pulmonic second sound as the left ventricle weakens with resultant increase in tension in the pulmonary circuit. Simultaneously, the aortic second sound may weaken.

X-Ray Findings.—It was seen above that concentric hypertrophy of the ...
of tl ...
does ...
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[illegible] he left ventricle, though more often it appears only when the whole heart fails. Marked alternation, which is readily detected by ordinary palpation of the pulse, is not common, but Gallavardin[a] and other recent authors have pointed out that the slighter degrees of the pulsus alternans are far more [illegible] Since reading their com- [illegible] alternation is best detected [illegible] ff is inflated above the sys- [illegible] in taking a blood-pressure reading The air in the cuff is then [illegible] let out while the observer listens for an interval below the systolic pressure in which only half the beats come through Gallavardin suggests another maneuver, not as [illegible]

[illegible] compression of the brachial artery. [illegible] and mercurials in the treatment of heart failure has become general, alternation of the pulse has become a rarity

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circuit. The right ventricle hypertrophies in response to the pulmonary

stasis, and there is thus maintained an increased pressure in the pulmonary circuit as long as the right ventricle is able to bear the increased burden—hypertension of the lesser circulation has developed, as Moschcowitz[67] so aptly puts it. Anatomically, hypertensive patients who have had a considerable stage of left ventricular insufficiency show brown induration of the lungs.

The most common evidence of this increased pressure in the pulmonary circuit is accentuation of the pulmonic second sound. *When in a patient with hypertension and an aortic second sound that has been louder than the pulmonic second sound, this is reversed so that the pulmonic second sound becomes the louder, we have an extremely valuable sign of failure of the left ventricle.* On several occasions I have been enabled to detect incipient failure of the left ventricle through this sign. In many hypertensive patients with cardiac asthma it is the only objective evidence of weakness of the left ventricle in the interval between the paroxysms of dyspnea. There may be the moist râles of pulmonary congestion at both bases, but these are often absent despite marked accentuation of the pulmonic second sound. Persistent cough with or without expectoration is not uncommon in patients with weakness of the left ventricle. The cough may be purely nocturnal. If there is sputum, heart failure cells can generally be found in it. Occasionally, the sputum is blood-streaked, and in rare instances larger quantities of blood are coughed up. Radiographic examination generally reveals indications of the increased vascularity of the lungs and during attacks of pulmonary edema may show diffuse clouding of the pulmonary fields.

A most important evidence of left ventricular failure is prolongation of the *pulmonary circulation time.* In practice this is usually determined by measuring the circulation time from the antecubital vein to the capillaries of the tongue. A substance which produces a strong taste (saccharin, decholin) is injected into an antecubital vein and the time is measured until the taste is perceived. In health this interval is between nine and seventeen seconds. In left ventricular failure the circulation time is prolonged, in extreme instances to over fifty seconds. The measurement of the decholin or saccharin[68] time is very simple, requires only an ampoule of decholin or soluble saccharin, a syringe and needle, and a watch, and furnishes information of great value to the clinicians. It is of especial help in differentiating the dyspnea of heart failure from that due to emphysema or bronchial asthma. However, there are exceptional cases with symptoms of left ventricular failure in which the circulation time is not definitely above the normal, apparently the hypertrophied right ventricle succeeds in maintaining the velocity of blood flow through the lesser circulation at almost normal, although at the expense of high pressure within the circuit.

Combined Left and Right Heart Failure.—Heart failure in essential hypertension usually sets in as the isolated left ventricular failure just described. Some succumb during the stage of uncomplicated left ventricular failure. But an even larger proportion of those whom we first see in the stage of isolated left ventricular insufficiency sooner or later develop the symptoms of failure of the right heart. And in some, a very small

minority in my experience, symptoms of both left and right sided failure are commingled from the start. *The ultimate goal ahead of most hypertensive patients who do not die of cerebral hemorrhage, uremia, or other non-cardiac causes is insufficiency of the whole heart.* Cardiac insufficiency may appear early in the disease or only after decades, it may come on suddenly or insidiously, with or without obvious exciting cause, but the danger of heart failure is always present and a cardiac death is the most frequent end of the individual with essential hypertension.

Pathogenesis of Right Heart Failure in Hypertension.—When the left side of the heart fails, the tension in the pulmonary circuit is elevated. The work of the right heart is correspondingly increased, with resultant hypertrophy. As lor [illegible]
greater resistance in [illegible]
uncomplicated failur[illegible]
cavæ and their tributaries [illegible] the right ventricle decompensates, *i. e.*, it fails to empty as completely as before, the diastolic tension within the chamber rises, and engorgement of the systemic veins is the consequence.

The pathogenesis of failure of the right ventricle in hypertension is probably most often similar to that of the antecedent failure of the left ventricle. The increased pressure in the pulmonary artery resulting from the latter and the consequent hypertrophy of the right ventricle necessitate a more ample coronary flow to the right ventricle than in health. As the individual myocardial fibers become thicker, their metabolic exchanges with the capillary blood are less efficient And at the same time progressive [illegible]

inadequate and decompensation occurs It is true that gross ischemic lesions of the right ventricle as a result of coronary arteriosclerosis are much less prominent than those of the left ventricle, but the nutrition of the right ventricle also suffers in widespread coronary arteriosclerosis The secondary causes of decompensation of the left ventricle (page 773) may likewise operate in causing insufficiency of the right side of the heart. Many individuals, especially among the elderly, with hypertension develop marked pulmonary emphysema, which serves further to increase the work of the right ventricle Likewise, the protracted and severe cough often present in the pulmonary engorgement of left ventricular failure adds to the strain on the right side of the heart Not rarely, auricular fibrillation or another arrhythmia precipitates insufficiency of the right side of the heart Flaxman[69] found that auricular fibrillation preceded and seemed to be concerned in the precipitation of about one-quarter of his

[illegible]

described by Bernheim,[70] and is know in the French literature as the *syndrome of Bernheim* In a large number of cases in which hypertension and arteriosclerosis had resulted in great dilatation of the left ventricle, and which succumbed with severe engorgement of the systemic veins,

Bernheim observed at necropsy that the right ventricle was not dilated. In these cases, he found that the cavity of the right ventricle was greatly compromised by the bulging into it of the greatly hypertrophied interventricular septum. In the course of the dilatation of the left ventricle, the interventricular septum bulged convexly to the right so far as to approach within a few millimeters of the right wall of the right ventricle in the apical half of the chamber. In some of his cases, little more than the upper half of the right ventricular cavity and the pulmonary conus remained open, the apical half of the right ventricle being represented only by a narrow slit between the bulging septum and the lateral wall. The pulmonary conus and the right auricle were dilated.

Bernheim's conception was that the bulging of the septum into the right ventricle, due to the dilatation of the left ventricle, so obstructs the flow of blood from the right auricle as to produce engorgement of the venæ cavæ with its consequences in the form of swelling of the cervical veins, high venous pressure, enlargement of the liver, etc. He observed that in these cases, contrary to mitral disease, the systemic venous engorgement is not accompanied by marked congestion of the lungs. Apparently, the interference with the filling of the right ventricle by the bulging septum serves to protect the lungs from the engorgement which would otherwise result from the failure of the left ventricle. Observations and deductions similar to those of Bernheim were published abroad by Mazzei[71] and others. In this country, Evans and White[72] were unable to convince themselves of the actuality of the Bernheim syndrome. However, Russek and Zohman[73] and Atlas[74] *et al* have published cases of the Bernheim syndrome which they suspected during life in hypertensive patients with evidences of severe right heart failure contrasting with little pulmonary engorgement, and verified at necropsy

At many necropsies on patients with hypertension or aortic regurgitation and severe systemic venous stasis, I have also observed that the septum of the enormously hypertrophied and dilated left ventricle bulged so far to the right that a large part of the cavity of the right ventricle was obliterated. These post-mortem appearances have often seemed to me to support strongly Bernheim's view that the bulging septum had actually interfered with the filling of the right ventricle during life, especially in the light of the great thickness and usual firmness of the septum. Moreover, when the left ventricle fails and dilates, the diastolic tension within it rises, which would further increase the resistance offered by a bulging septum to the filling of the right ventricle

It is interesting that a similar conception was attained by Henderson and Pri [illegible]
fou [illegible]
anc [illegible]
of t[illegible] ment of the interventricular septum so as to interfere with the filling of the right ventricle.

Septal bulging would explain the occasional cases in which left ventricular dilatation due to hypertension or aortic regurgitation is accompanied by systemic venous engorgement in the absence of severe pulmonary conges-

tion. In a number of patients with hypertension, I have observed elevation of the brachial venous pressure to even 20 cm. of water in the absence of notable pulmonary engorgement and where the pulmonary circulation time was little prolonged. An important feature of such cases, as pointed out by R[illegible] lung fields in the roentgen picture. [illegible]
the left ventricle and little of the rig[illegible]
Atlas et al. believed they demonstrated by x-ray examination enlargement of the left ventricle and right auricle, with little change in the left auricle and right ventricle. It would seem very probable that in such cases the venous engorgement is due to bulging of the septum into the right ventricle, a virtual tricuspid stenosis.

It would thus appear that two mechanisms may result in systemic venous engor[illegible] hypertension:

1. [illegible]

ventr[illegible]

i[illegible]

[illegible]

Further investigation is needed regarding the participation of these two mechanisms of systemic venous engorgement in essential hypertension. It has seemed to me that obturation of the right ventricle by septal bulging is more common in the relatively young in whom hypertrophy of the left ventricle is more pronounced Angiocardiography may throw light on the importance of the Bernheim syndrome.

Signs of Universal Cardiac Failure —The failure of the right ventricle and then of the right auricle is accompanied by dilatation of these chambers. The dilatation of the right auricle results in enlargement of the heart to

[illegible]

right border may be almost as far from the mid-line as the left. This is also true in the not infrequent cases of complication of essential hypertension by emphysema The result of the universal hypertrophy and dilatation of all the chambers in far-advanced cardiac failure of essential hypertension is thus the production of very large hearts, enlarged in all diameters. In the roentgenogram, such hearts are often of somewhat spherical shape, while in other instances the borders are rather straight, resulting in a triangular outline They may seem spread out on the diaphragm and give the impression of diminished tonicity, the differentiation of the individual segments of the borders being lost. In the fluoroscope the pulsation is very slight The appearance is similar to that seen in the last stages of valvular or coronary artery disease in which there is likewise universal dilatation of all the chambers, so that seeing the roentgenogram only in this last stage, one could not say it belonged to a hypertensive heart

While arrhythmias are rare during the stage of uncomplicated left ventricular failure in hypertension, they are common in the later stages of cardiac insufficiency. Contrary to an opinion formerly held, auricular fibrillation is common and often precipitates right heart failure. Rothstadt[76] found auricular fibrillation in 73 of 1000 patients with essential hypertension uncomplicated by mitral stenosis, and White[77] in 92 of 708. In 800 patients with hypertensive heart disease, Flaxman[69] observed auricular fibrillation in 198 and extrasystoles, most often ventricular, in 28. Auricular, nodal and ventricular tachycardias and varying degrees of heartblock occur in rare cases, evidently as manifestations of damage to the myocardium by coronary artery disease. The heart-block may result in Stokes-Adams syndrome. Essential hypertension complicated by heart-block is not to be confused with the compensatory systolic hypertension sometimes present in heart-block of any origin, which is accompanied by diastolic hypotension. The pulsus alternans has already been discussed.

The peripheral manifestations of the failure of the hypertensive heart do not differ from the banal findings in valvular and other cardiopathies, and need not detain us long. Dyspnea, cyanosis, edema, transudation into the serous cavities, congestion of the lungs, swelling of the liver and increased venous pressure are all commonly found in severe failure of the hypertensive heart. It is, however, remarkable how long some patients with essential hypertension remain apparently at the brink of well-marked cardiac decompensation without actually becoming severely decompensated. For months, they may have swelling of the ankles toward evening which clears up during the night. The same moderate degree of dyspnea on exertion or even well-marked swelling of the liver may last for months or even years while the patient is ambulatory without changing notably. Ultimately, unless there is satisfactory response to treatment or they die of some other cause, these individuals develop the typical picture of severe myocardial insufficiency with orthopnea, great edema, huge liver, etc. But since the general introduction of drastic sodium restriction and mercurials, the duration of life in essential [illegible] heart failure has greatly increas[illegible] succumbed to congestive failure [illegible] some other complication sets in.

Effect of Cardiac Failure on Hypertension.—Cardiac failure in hypertension, as was mentioned above, may be accompanied by a fall in blood pressure. The drop in blood pressure affects the systolic more than the diastolic pressure, but the latter may also be markedly lowered. In fact, the arterial tension in severe cardiac failure may drop to normal or subnormal levels. When cardiac failure in other than moribund hypertensive patients is accompanied by a sudden and great fall in blood pressure, it usually indicates that the cause of the heart failure is myocardial infarction. In such cases, the blood pressure may drop to dangerously or even fatally low levels. Cardiac failure not due to myocardial infarction is usually accompanied by much less of a drop in blood pressure, if, indeed, there is any fall whatsoever. I have repeatedly observed this difference, the explanation of which is obscure. The factor of shock participates only in the first weeks after myocardial infarction and does not explain the permanent lowering of the blood pressure in many patients.

Fall in blood pressure, then, ... far from a constant manifestation of cardiac failure in hypertension. ... are severely dyspneic and edema ... at its previous high level. In these ... high blood pressure, there is doubtless a lessened output of the heart, but the peripheral vessels are so constricted that the small output serves to ... the high blood pressure (cf. Poiseuille's law, page 296). ... times actually ... lial insufficiency ... d digitalization ... as shown by clearing up of the edema, ... of the swollen liver, etc. This phenomenon (which was observed before the introduction of mercurials) was first described by Sahli[18] and termed by him *high-pressure stasis* (Hochdruckstauung). Meyer and Mullen[19] found that in 16 of 35 patients with severe cardiac decompensation due to various causes, the blood pressure fell as the function of the heart improved. Sahli thought that when a rise in pressure accompanies the failure of the heart, it is due to constriction of the peripheral vessels as a result of pulmonary engorgement (i.e., presumably, by increased carbon dioxide content of the blood). This explanation would seem very plausible for the acute rise in blood pressure that often accompanies cardiac asthma with pulmonary edema (page 780). To ... maintenance of ... tension may be at least partly ... increased blood volume that accompany chronic heart failure. When the heart failure improves as a result of bed rest, salt restriction, digitalis and mercurial diuretics, sodium is excreted and blood volume decreases with concomitant fall in arterial pressure.

CORONARY ARTERY DISEASE AND ANGINA PECTORIS

The large majority of patients with essential hypertension develop arteriosclerotic changes of the coronary arteries. These may be but slight, but more often they are well marked and not uncommonly extremely severe. Bell and Clawson[20] found that only 10 per cent of hypertensive hearts have no notable coronary arteriosclerosis, while in 55 per cent there is a moderate degree, and in 35 per cent a severe degree of coronary arteriosclerosis. Davis and Klainer[21] observed that the incidence of severe coronary arteriosclerosis is 76 per cent greater in essential hypertension than in controls. Nevertheless, they do not believe ... ... normotensives, Davis and Klainer found coronary arteriosclerosis much more common in men with essential hypertension below the age of sixty years than in hypertensive women of corresponding age. Symptoms of coronary disease are much more common in males than in females with hypertension before the age of sixty, a fact which is sometimes of aid in diagnosis. As a rule, the arteriosclerosis of the coronary arteries is best marked in the branches supplying the left ventricle, the chamber which bears the initial strain in hypertension.

It is, therefore, not surprising that the course of many cases of essential hypertension is determined by the lesions of the coronary arteries. Not at all uncommonly, the first symptom that brings the hypertensive patient to the physician is cardiac pain. An individual who never knew he had hypertension may succumb to a coronary occlusion, the causative essential hypertension being revealed at necropsy by the presence of arteriolosclerotic kidneys. In many instances, the entire clinical picture of essential hypertension is dominated by anginal attacks appearing at intervals during many years, until death finally occurs relatively suddenly from occlusion of a large coronary branch or more gradually after a long period of myocardial insufficiency produced by widespread myomalacia cordis consequent on diffuse narrowing of the coronary radicals.

Symptoms of Coronary Arteriosclerosis in Essential Hypertension.—Until a few years ago there were many clinicians, including Allbutt[82] and Libman,[83] who believed that anginal pain in essential hypertension does not necessarily bespeak coronary arteriosclerosis, but may result from cardiac strain or disease of the aorta. Thus, Libman, who had great necropsy experience, summarized his observations in the statement that cardiac pain may be due to "hypertension with or without dilatation of the arch of the aorta, and with or without narrowing of the orifices of the coronary arteries." Nevertheless, the occurrence of angina pectoris in a patient with essential hypertension in the absence of arteriosclerotic narrowing of the coronary arteries must be a rarity. In fact, narrowing of the coronary arteries has been present in every instance of essential hypertension with definite anginal pains that I have had the opportunity of examining at necropsy. For this reason I believe that the occurrence of anginal pain in a hypertensive warrants the diagnosis of coronary arteriosclerosis. Of course, such causes of cardiac pain as psychoneurosis, syphilitic aortitis, rheumatic aortic regurgitation and anemia must be ruled out That hypertension *per se* does not cause angina pectoris is shown by its absence in nephritic hypertension. Since the only established mechanism of anginal pain is myocardial anoxia, it might be anticipated that the hypertrophied heart of essential hypertension with its great oxygen requirement would develop such pain as a result of relatively less impairment of coronary flow than would a normotensive. This inference is supported by the investigations of Davis and Klainer, who found that the severity of coronary arteriosclerosis in patients with angina pectoris averages much less when they are hypertensive. My experience has been the same.

The clinical picture of coronary artery disease in patients with essential hypertension does not differ materially from that encountered when the coronary sclerosis is not associated with high blood pressure. One meets with all the innumerable gradations of cardiac pain, from a slight feeling of tightness in the chest following vigorous exercise to the full-blown anginal seizure with agonizing pain and sense of constriction associated with the fear of death. Despite the high blood pressure, coronary thrombosis is an ever-present danger in patients with essential hypertension, including the relatively young. Evidences of hypertension were present in 34 per cent of Conner and Holt's[87] cases of coronary thrombosis. But the incidence of myocardial infarction is less in angina in hypertensives than in

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arteriosclerosis is concern
the hypertensive heart. . . .
pear as myocardial insufficiency appears; this is, perhaps, due to forced curtailment of the activities of the patient. When auricular fibrillation develops, the anginal pains generally ameliorate or vanish.

As mentioned above, myocardial injury due to coronary artery disease

Coronary insufficiency or occlusion may reduce previously high pressure to normal or subnormal levels even though the general condition of the patient is not that of collapse. Following the coronary closure, the blood

patient's life, despite the fact that he recovers sufficiently to be up and

and occur in coronary artery disease without past hypertension. At necropsy, the previous existence of hypertension in such cases may be demonstrated by the presence of arteriolosclerotic kidneys

VALVULAR LESIONS WITH ESSENTIAL HYPERTENSION

Valvular lesions are common complications of essential hypertension Thus, Boas and Fineberg[84] found that 8.4 per cent of 403 patients with hypertension also had mitral stenosis. This agrees well with the post-mortem observations of Pitt, which they quote, who found mitral stenosis
nd Fineberg
ypertension,
. . . . . . of patients over forty-five years of age with mitral stenosis had high blood pressure The recent observations of Roseman and Wasserman[85] . . .
it hyper-
in other
. . . of the mitral stenosis group and 43 1 per cent of other hospital patients Aortic insufficiency also not infrequently complicates essential hypertension. In the case of aortic insufficiency, of course, one must guard against considering the purely systolic hypertension due to the valvular

lesion as a true (*i.e.*, diastolic) hypertension. Since children and young adults with valvular defects do not have hypertension, unless there is complicating glomerulonephritis, the valvular disease cannot be regarded as the cause of the hypertension. Actually, the combination of valvular

may be present, the most frequent combination being that of mitral stenosis with essential hypertension in women about the time of the menopause.

2. The valvular lesions are arteriosclerotic. In these cases the hypertension is undoubtedly of great importance in the production of the valvular lesions, much as it favors the occurrence of arteriosclerosis of the vessels. In fact, at necropsy arteriosclerotic changes of the valves are to be found in most individuals who had long-standing hypertension. Of 16 cases of aortic insufficiency complicating hypertension studied by Boas and Fineberg, 10 were arteriosclerotic. On the other hand, mitral stenosis complicating essential hypertension is probably almost always, if not always, of rheumatic etiology. While Boas and Fineberg regarded 1 of their 11 cases of mitral stenosis with essential hypertension as arteriosclerotic, Levine and Fulton did not observe this etiology.

3. The valvular lesion is aortic insufficiency of syphilitic etiology. We have already referred to the fact that the combination of syphilitic aortitis with essential hypertension is by no means rare in population groups with a high incidence of lues (page 746).

One is struck in many of the cases, other than the syphilitic, by the fact that the valvular lesion seems to add little additional strain to that already thrown on the heart by the hypertension. This is especially true of the arteriosclerotic valvular lesions, which are generally of little clinical importance But also, particularly in women, mitral stenosis of rheumatic origin and essential hypertension may coëxist for years without the appearance of myocardial insufficiency In these cases, heart failure is apt to be precipitated by auricular fibrillation. It is also worthy of mention that marked narrowing of the mitral ostium does not in itself inhibit the development of even extreme hypertension. I have several times seen very tight mitral stenosis at the necropsy of a patient who had a systolic blood pressure of well over 200 mm This is in accord with the fact, previously mentioned, that even with a very small cardiac output, constriction of the peripheral arterioles can maintain a high blood pressure The combination of essential hypertension with syphilitic aortitis and aortic insufficiency seems particularly apt to cause sudden myocardial insufficiency However, I have seen a number of such cases in which the two diseases have been present for several years without incapacitating the patient.

THE ARTERIES IN ESSENTIAL HYPERTENSION

Thayer and Fabyan[88] found that in hypertensive individuals the intima and media of the radial artery are almost uniformly thicker than the average Nevertheless, cases of essential hypertension are not rare in which

at post-mortem examination little or no more arteriosclerosis is found than would be expected at the age of the patient. More often, however, there is well-marked general arteriosclerosis which in many instances, particularly when diabetes has been present for a long time, attains an extreme degree. In such cases, the consequences of arteriosclerosis in one organ or another ... to the clinical picture. From a clinical point of

... the sections on the particular organs.

The Aorta.—Arteriosclerosis of the aorta is often of high degree in hypertensive patients In such cases, the aorta is elongated and dilated. The upward displacement of the arch resulting from the elongation and dilatation may cause a palpable pulsation behind the manubrium. The ... and great vessels also often leads to the ...

Rowntree[59] and may lead to the mistaken suspicion of aneurysm. ... often dulness to either side of the manubrium, though such dulness is not uncommonly present, particularly to the left, when the roentgen examination does not reveal a notable broadening of the vascular shadow In ... be due to closer approxi- ... On auscultation, there is ... the second sound, the interpretation of which has already been discussed (page 272) The sclerosis of the root of the aorta often leads to an aortic systolic murmur. The loud second sound and absence of a thrill differentiate the murmur from one due to aortic stenosis

The roentgen examination reveals a prominent knob at the junction of the transverse and descending arches, which often pulsates strongly; occasionally, calcification can be made out at the border of this knob. Only when the arteriosclerotic elongation and dilatation are of high degree is the shadow of the ascending aorta broadened notably to the right, so ...

in which it can sometimes be detected when dorso-ventral illumination does not reveal the widening Dynamic dilatation of the ascending aorta is sometimes so prominent in younger hypertensives as to simulate aneurysm, it does not bespeak arteriosclerosis

Very important is the effect of marked arteriosclerosis of the aorta and its primary branches on the blood pressure Because of the diminished elasticity of the arteriosclerotic aorta, less blood is stored in the vessel immediately after systolic ejection from the left ventricle, and during diastole the elastic recoil of the aorta is less forceful The result is that aortic arteriosclerosis tends to raise the systolic and lower the diastolic pressure, with consequent increase in pulse pressure This is probably the explanation of the fact that elderly patients with essential hypertension tend to have a higher pulse pressure and lower diastolic pressure than younger hypertensives In consequence of aortic arteriosclerosis, such

readings. [illegible] essential hypertension. [illegible] elasticity of the aorta may produce an elevated systolic pressure even though the subject does not have what is here known as essential hypertension (page 295).

It has already been mentioned that the arteriosclerotic process may involve the aortic cusps and thereby cause aortic insufficiency, revealed by an aortic diastolic murmur. Arteriosclerosis, like syphilis, rarely if ever causes well-marked aortic stenosis; the presence of aortic stenosis indicates previous rheumatic disease of the valve. Arteriosclerotic aortic insufficiency is rarely so marked as to cause any of the peripheral phenomena so prominent in syphilitic and particularly rheumatic aortic insufficiency. It is to be remembered that marked arteriosclerosis of the aorta without aortic insufficiency may cause a purely systolic hypertension with increased pulse pressure. Occasionally, differences in the pulses on the two sides with retardation of the smaller pulse are caused by involvement of the mouth of one of the great branches by the arteriosclerotic process in the aorta, or such differences are, much more rarely, due to narrowing in the course of one of these vessels. However, the frequency of differences in blood pressure on the two sides is to be borne in mind (page 257).

Arteriosclerosis of the aorta apparently does not cause any notable symptoms, except in the extremely rare instances of large arteriosclerotic aneurysm or of embolization of thrombi from atheromatous ulcers. Such anginal pains as occur in patients with arteriosclerosis of the aorta are due to the coronary sclerosis that is generally also present. According to the investigations of Fahr and Davis,[90] an increment in the rigidity of the arteries does not in itself increase the work of the heart.

Arteriosclerosis of the Extremities.—Arteriosclerosis affects the arteries of the extremities to a varying extent in essential hypertension. There are many cases of hypertension, even of long standing, in which palpation of the radials, brachials, and other accessible arteries reveals no notable arteriosclerosis. On the other hand, the peripheral arteriosclerosis may be extreme, especially when the hypertension occurs under circumstances which in themselves predispose to arteriosclerosis—in the very old, the diabetic and the gouty. The changes in the peripheral arteries in hypertensive patients may be either the usual intimal lesions of arteriosclerosis or Moenckeberg's medial calcification. When the sclerotic thickening is great, and particularly when there is marked calcification, the changes in the accessible arteries are readily detected by palpation. But when the arteriosclerotic changes are less extreme, the palpatory findings, as Fischer and Schlayer[91] and Moschcowitz[92] have pointed out, may be very deceptive

Fischer and Schlayer found that in one-half the cases in which postmortem examination revealed intimal thickening in the radial artery, the thickening was not recognized during life Furthermore, no arteriosclerosis was found in three-fourths of the instances in which the radial artery seemed thickened to palpation. Fischer and Schlayer believe the feeling of thickening is in most instances due to the media. In some cases there is actual thickening of the media, while in others a functional hypertonus is responsible. Moschcowitz also emphasizes that functional hypertonus may simulate thickening and terms the condition "pseudo-arteriosclerosis."

that should always be looked for in patients ...
Sometimes, calcification of the vessels of the extremities is seen in the roentgen picture when the change is not appreciable to palpation.

Symptoms of Arteriosclerosis of the Extremities.—Arteriosclerosis of the vessels of the extremities causes well-marked symptoms in many patients with essential hypertension Such manifestations of peripheral arteriosclerosis may first bring the patient to the physician and thus lead to the discovery of the hypertension, or they may appear only after the hypertension has been known to exist for years. Sometimes, particularly when the hypertension is associated with diabetes, the consequences of peripheral arteriosclerosis may completely dominate the clinical picture; despite the high arterial pressure, the circulation through the narrowed or closed peripheral vessels is inadequate.

... pointed out that paresthesia and coldness of the

among his "petits signes du brightisme (minor symptoms of ... disease) Bauer[94] has also called attention to the frequency of rheumatoid symptoms in hypertensive patients, speaking of "Hochdruckrheumatismus" (high-pressure rheumatism). I have been much impressed with how often these symptoms occur in dispensary practice; they are most common in the lower extremities Such patients, as Bauer points out, are often treated for long periods for muscular rheumatism, chronic arthritis, neuritis, etc. However, these pains, paresthesias, cramps, etc., in hypertensive patients are probably, as a rule, of arteriosclerotic origin, being associated with marked peripheral arteriosclerosis and often with a feeble or absent pulse in the dorsalis pedis and other vessels of the lower extremities Objective evidence of the circulatory disturbance in the extremities is often present in the form of coldness, cyanosis (in the absence of myocardial insufficiency), alternating pallor and flushing of the distal parts, or cutis marmorata It should be remembered, however, that rheumatoid arthritis or osteoarthritis may occur in a patient with essential hypertension, though in my experience the complication in marked form has been rare

sclerosis, perhaps for the reason that such individuals usually also have

pains and paresthesias in the extremities of some patients with essential hypertension develop on an arteriosclerotic basis, it seems probable that in many instances there is also an angiospastic element. This explains the

readings as 210/80 mm. are not rare in older patients with essential hypertension. It should be borne in mind that diminished elasticity of the aorta may produce an elevated systolic pressure even though the subject does not have what is here known as essential hypertension (page 295).

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Popovici[200] have recently supported the conception that emphysema in the elderly may lead to hypertension—which they term phrenic hypertension—through the intermediacy of loss of negative intrapleural pressure, consequently increased venous pressure and congestion of the kidneys, but the thesis hardly seems proved The emphysema throws additional strain on the right heart, and in such patients the right heart may be almost as much hypertrophied as the left The clinical picture may then differ little from that of uncomplicated cor pulmonale Cough and dyspnea on exertion are usually the chief complaints and the course of the disease is determined by how well the heart holds out The duration of a considerable degree of myocardial insufficiency in patients with both essential ... remarkable, such individuals may

in the final myocardial insufficiency or other modes of ending of essential hypertension, though less so than *before the introduction of antibiotics* In most of the cases in which so-called bronchopneumonia complicates the left ventricular failure of essential hypertension, the pulmonary process originates in infarction When primary atypical or the now rare lobar pneumonia complicate essential hypertension without heart failure, the course does not differ from that in normotensives and the prognosis is almost as good

does occur, as has been mentioned, the tuberculous lesion is almost always of the fibroid type with little or no tendency to progression

THE NERVOUS SYSTEM IN ESSENTIAL HYPERTENSION

Only a minority of patients with essential hypertension run the course of the disease without the appearance of symptoms attributable to the nervous system However, the prominence of the nervous manifestations varies greatly from case to case, in some instances, they are the dominant feature throughout the clinical course, while in others there are few or no

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cold and numbness which may deepen to intense pain. Sometimes, it is observed that the affected finger is intensely pale. The changes pass away, usually after a few minutes, as quickly as they came. Dieulafoy observed "dead fingers" as an initial symptom in Bright's disease. Typical dead fingers are rare, but the existence of transitory pains and numbness in the fingers, to which the patient pays little attention, can often be elicited in the history.

Syndromes akin to those of the so-called *vasomotor neuroses*, as Raynaud's disease and erythromelalgia, are encountered in unusual instances of essential hypertension, 4 such cases having been observed by Westphal.[28] However, in the vast majority of instances of true Raynaud's disease the blood pressure is within normal limits, except that during the actual attacks, especially when very painful, there may be transitory slight elevation.

THE LUNGS IN ESSENTIAL HYPERTENSION

The elevation of pressure in the arteries of the systemic circulation is not necessarily accompanied by an increase in the blood pressure in the ...

... who die without failure of the left ventricle, for example, of cerebral hemorrhage. But with failure of the left ventricle, there occurs stasis and increase in pressure in the pulmonary circuit, as evidenced clinically by accentuation of the pulmonic second sound and at necropsy by brown induration of the lungs and hypertrophy of the right ventricle Since the introduction of cardiac catheterization, the rise in pulmonary artery pressure in left ventricular failure, long assumed on the basis of the foregoing evidence, has been proved directly. Borden *et al.*[95] found that while the pulmonary artery pressure in health averages 20 mm systolic and 9 mm. diastolic, in 23 patients with left ventricular failure (in 11 due to hypertension), it averaged 38/18 mm If pulmonary hypertension lasts long enough, a certain degree of pulmonary arteriosclerosis may develop, though this is rarely marked. The mechanism of the right ventricular hypertrophy and pulmonary arteriosclerosis in essential hypertension is thus quite analogous to that in mitral stenosis.

Hemoptysis in Essential Hypertension.—Chronic passive congestion of the lungs produced by the above mechanism in essential hypertension may be manifested by cough and even by occasional streaky sputum. This is particularly often the case when marked emphysema is also present. Frank hemoptysis is decidedly unusual in essential hypertension, but I have seen very copious bleeding from the lungs in several hypertensive patients in whom no other cause than left ventricular failure with chronic passive congestion and probable infarction could be found. In one patient with essential hypertension, in fact, hemoptysis proved fatal; though no necropsy was obtained in this case, the roentgen-ray examination revealed

. Nor is it due to im-
parallelism between the
incidence of headache and the height of the ... pressure. Headaches which have been present for years may disappear in the absence of change in blood pressure. Headache may vanish after sympathectomy even though the operation has little or no effect on the blood pressure. In the except ... in which patients with severe headache develop heart failure
arteri

Wolff's[109] investigations are interpreted by ...

tions that in both migraine and hypertension there is no increase in the amplitude of pulsation of the intracranial arteries during the headache or decrease during subsidence, and that the headache is alleviated by ergotamine tartrate, which he states acts chiefly on the branches of the external carotid artery However, in the experience of the writer ergotamine tartrate has had little effect on most headaches in hypertensives, nothing like what one so often sees in migraine Wolff also believes that some of the headaches of hypertensives are due to sustained contraction of skeletal muscles of the head and neck

the blood pressure falls on bed rest, sodium restriction, hypotensive drugs,
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amelioration It is not uncommonly associated with nausea, vomiting, and stiffness of the neck, since papilledema is also present, the clinical picture simulates that of brain tumor. Actually, as measurement of the

... long periods in a few cases by subtemporal decompression. Shellburne

symptoms attributable to the nervous system. In a general way, it seems to be true that in those cases which start with cardiac insufficiency the nervous symptoms are apt to be but minimal, while in those in whom the disease is ushered in by nervous symptoms, the heart usually holds out for a long time or to the very end. Thus, in essential hypertension appearing at the time of the menopause, the nervous symptoms are usually dominant and despite the irrepressible activity of most such patients, one is often surprised to see how well the heart holds out against great hypertension for many years. In patients whose activities are curtailed by the occurrence of hemiplegia early in the clinical course, the usual absence of cardiac insufficiency is readily conprehensible. However, there are many exceptions in which cardiac as well as nervous symptoms are prominent; this is particularly true of those patients with arteriosclerotic disease of both brain and heart.

Headache.—Headache is a symptom from which a majority of patients with essential hypertension suffer at one time or another. Robey[97] found that 230 of 448 patients with hypertension had had headache, but in my experience the incidence of headache in true (diastolic) essential hypertension has been higher. Cephalalgia is frequently the initial complaint. In fact, it is common to elicit in the past history of patients with essential hypertension that they have suffered with migraine since childhood (page 760), long before the hypertension could have been present. In such cases, however, the patient usually states that the headache changed in character when the hypertension appeared. The headache may be occipital, frontal or in any part of the head, sometimes, it is unilateral as in migraine. When very severe, the headache may radiate down the back of the neck to the trapezius region and shoulders; such patients may be regarded as suffering from cervical spondylitis or some other skeletal disorder and not rarely go for osteopathic treatment. Visual, auditory or other aura may precede the headache, and nausea and vomiting may accompany it, thus increasing the resemblance to migraine. However, the latter phenomena are rare. The headache may be merely a dull ache or feeling of pressure, or it may attain the utmost severity and last for days at a time Often, it is distinctly throbbing. A very frequent type of headache—so common that Janeway[1] terms it the "typical" headache—is one which is present when the patient awakens in the morning or wakes him prematurely, reaches its maximum intensity before breakfast, and disappears during the course of the morning after he gets about This may recur daily for long periods. The early morning headache of hypertensives is sometimes prevented or alleviated by sleeping with the head of the bed elevated (MacLean and Allen,[98] Steiner,[99] own observations).

The pathogenesis of [illegible]
from (1) the headaches [illegible]
intracranial pressure fr[illegible]
there are evidences of brain damage due to cerebral arteriosclerosis and the headache is correlated with the arteriosclerosis.

In the "benign" phases of essential hypertension, the cerebrospinal fluid pressure is normal (unless there is right heart failure with high venous pressure, and in such cases headache is rarely severe). The headache is

Hypertensive Encephalopathy.—A striking phenomenon in some cases of essential hypertension is the appearance of manifestations of hypertensive encephalopathy due either to cerebral angiospasms or to edema of the brain [illegible] long

Cerebral Angiospa[illegible] clero-
standing "benign" [illegible] cerebral angiospasms may [illegible] hypertension, but they are [illegible] rence of evanescent palsies, amaurosis, aphasia, etc., in hypertensive and arteriosclerotic individuals was pointed out long ago by Peabody,[106] and a masterful clinical study devoted to them by Osler,[107] who observed many transient attacks of aphasia, hemiplegia and monoplegia in his friend, Dr. George Ross. A number of names have been applied to these striking cerebral episodes by different authors—cerebral vascular crises by Pal,[108] chronic pseudo-uremia by Volhard[109] The evidence which suggests that these transitory cerebral phenomena are due to cerebral vasoconstriction and they are, therefore, included under the concept of hypertensive encephalopathy, was presented in Chapter 11, additional post-mortem observations con-[illegible]s are recorded by [illegible] of angiospasm in [illegible] is rare in essential hypertension, Paullin *et al*[110] observed transient cerebral phenomena in 11.2 per cent of their hypertensive patients, though it is not probable that all of these were actually manifestations of hypertensive encephalopathy. Among the phenomena in question are transient hemiplegia, monoplegia, aphasia, amaurosis and other focal cerebral symptoms, possibly, some of the instances of syncope in hypertensive patients are to be included here The hemiplegia, aphasia, or other cerebral symptom comes on suddenly and often without any obvious exciting cause. Sometimes the onset is while the patient is in bed It was mentioned in Chapter 11 that the cerebral episode is often preceded by a well-marked rise in blood pressure The symptoms may last from a few minutes to many hours, and clear up quickly and completely Many of the episodes are so brief that unless special inquiry is made, they will not be mentioned by the patient. In the following case, the history of the cerebral episode was obtained only after specific questioning·

A colored woman with very high blood pressure walked into a grocery store to buy some bread Suddenly, she realized, though her mind was perfectly clear, that she could not ask for what she wanted She pointed to the bread, took and paid for it, and walked home. When she reached her home, she regained the power of speech She had also had several transitory monoplegias

An individual may have many seizures, one of Osler's patients had twenty attacks of aphasia After several such transitory attacks occurring at considerable intervals with complete recovery from each, a permanent hemiplegia, aphasia, etc , may finally result. In such instances, it may be

et al.[101] found headache present in 16 of 20 hypertensive patients with elevated spinal fluid pressure, but in only 12 of 30 with normal spinal pressure.

Vertigo.—This is also a common symptom in essential hypertension, particularly in women. Sometimes it is one of the chief complaints, or else the dizziness may be but slight, perhaps appearing only when the patient rides in an elevator or first sits up in bed in the morning. *Tinnitus aurium* may be very annoying. There are unusual cases in which the vertigo and tinnitus occur in severe attacks akin to the Ménière symptom-complex.

Irritability.—Individuals with essential hypertension are often extremely irritable. Restlessness, impatience, depression and irritability are among the most common complaints at the first visit of hypertensive patients to the physician. Sometimes, they have been regarded as "nervous" all their lives, but in other instances the nervousness appears only with the development of the hypertension. They worry without adequate cause, are unable to concentrate on mental work, and have emotional outbursts. Insomnia is a very frequent complaint. Often the insomnia is of the type in which the patient falls asleep readily enough but awakens too early and cannot go to sleep again. The patients become unable to face the realities of life, become depressed and may go into melancholic states. The existence of clinical pictures in essential hypertension simulating a psychoneurosis is worthy of emphasis, for they are relatively common and often misunderstood. It may be difficult or impossible in a hypertensive patient to decide whether seemingly psychoneurotic symptoms are independent of the hypertension, play a part in the causation or aggravation of the latter, or are a manifestation of the hypertensive disease It should be borne in mind that in a patient with long-standing essential hypertension, cerebral arteriosclerosis may evolve insidiously and produce symptoms simulating a psychoneurosis ("arteriosclerotic pseudo-neurasthenia" of Bing) [102]

Page's Hypertensive Diencephalic Syndrome.—Page[103] has pointed out that among the clinical pictures presented by patients with essential hypertension is an aggregation of symptoms similar to what might be anticipated from stimulation of the diencephalon, although the actual operation of this mechanism has not been demonstrated. It usually occurs in young or middle-aged women, only rarely in men The patients are very emotional and subject to unmotivated crying The blood pressure is extremely labile Especially striking is the occurrence of episodes in which a deep blush often covered by beads of perspiration extends over the face and chest accompanied by cold and mottle extremities, tremulousness, tachycardia with the subjective sensation of palpitation, and frequent lachrymation. Page noted that the clinical picture has many features in common with Graves' disease including a basal metabolic rate up to plus 30 per cent (I have seen even higher in cases proved not to be hyperthyroid by radio-iodine studies and Vorzimer's[104] urinary pigment ratio). The episodes may be brought on by emotion. Page has found that patients with his clinical picture have an excellent prognosis as regards duration of life, with which my own experience accords.

encephalopathy due either to cerebral angiospasms or to ... brain

Cerebral Angiospasms.—These usually occur in older patients with long standing "benign" hypertension and widespread and severe arteriosclerosis. Russek and Zohman[105] have shown that cerebral angiospasms may also occur in arteriosclerosis in the absence of hypertension, but they are far rarer with normal blood pressure. The occurrence of evanescent palsies, amaurosis, aphasia, etc , in hypertensive and arteriosclerotic individuals was pointed out long ago by Peabody,[106] and a masterful clinical study devoted to them by Osler,[107] who observed many transient attacks of aphasia, hemiplegia and monoplegia in his friend, Dr. George Ross. A number of names have been applied to these striking cerebral episodes by different authors—cerebral vascular crises by Pal,[108] chronic pseudouremia by Volhard.[109] The evidence which suggests that these transitory cerebral phenomena are due to cerebral vasoconstriction and they are, therefore, included under the concept of hypertensive encephalopathy, was presented in Chapter 11; additional post-mortem observations con- ...s are recorded by ... of angiospasm in

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An individual may have many seizures, one of Osler's patients had twenty attacks of aphasia After several such transitory attacks occurring at considerable intervals with complete recovery from each, a permanent hemiplegia, aphasia, etc., may finally result. In such instances, it may be

that repeated ischemia of the particular part of the brain has finally led to irreversible changes; or else that thrombosis of the vessel has occurred.

Cerebral Edema.—In the malignant phase of essential hypertension, the brain may become edematous with consequent rise in intracranial pressure. The elevated intracranial tension is revealed by papilledema and increased spinal fluid pressure. In addition there may be other manifestations of the increased intracranial tension. Of these, headache is much the most common. But there may also be nausea, projectile vomiting, stiffness of the neck, and impairment of vision due to choked disk. The latter may attain an elevation of six or more diopters. Attacks of epileptiform convulsions followed by coma and differing in no wise from those of eclampsia gravidarum may occur. Cheyne-Stokes breathing often appears in the last stages. The patient may finally go into prolonged and ultimately fatal coma which is not uremic. In some instances of the malignant phase of essential hypertension these consequences of increased intracranial pressure due to edema of the brain completely dominate the clinical picture, which simulates closely that of brain tumor, and is ameliorated only by measures which decrease intracranial tension This "pseudo-tumoral" picture may last for months

The Cerbrospinal Pressure.—There is no constant relation between the arterial blood pressure and the tension of the cerebrospinal fluid; the latter may be within normal limits despite maximal arterial hypertension. However, in some patients with essential hypertension the cerebrospinal pressure is elevated. As far as I have observed, this does not occur in the "benign" phases of the disease without hypertensive neuro-retinopathy, unless there is failure of the right heart, which raises the intrathecal tension through the intermediacy of high venous pressure. On the other hand, the cerebrospinal pressure is elevated almost constantly in the malignant phase of essential hypertension, as revealed by hypertensive neuro-retinopathy. Thus, Shelb

tension and

made similar

sequence of events in such cases is that extreme hypertension produces edema of the brain, which in turn elevates the intracranial pressure and thus produces both papilledema and elevated spinal fluid pressure. However blurring of the disc margins may also occur as part of hypertensive retinopathy in the absence of increased cerebrospinal fluid pressure The spinal fluid pressure in the malignant phase of essential hypertension often exceeds 30 cm. of water and very rarely even 40 cm The relations of the cerebrospinal pressure in essential hypertension to the retinal lesions and the occurrence of headache are discussed on pages 379 and 827 It may be remarked that renal insufficiency does not of itself elevate the cerebrospinal pressure, I have several times found the latter normal during uremia due to primary renal disease.

CEREBRAL HEMORRHAGE IN ESSENTIAL HYPERTENSION

It has long been known that there is a correlation between left ventricular hypertrophy and cerebral hemorrhage, in fact, this association was observed

at the necropsy of Malpighi,[112] who died in an apoplectic stroke. Senhouse Kirkes[113] found that 17 of 22 individuals who had succumbed to cerebral had left ventricular hypertrophy. The connecting link be-

14 per cent of the fatalities in Janeway's patients with hypertension. The vast majority of instances of cerebral hemorrhage occur in individuals with arterial hypertension; in fact, Lippmann[114] found that hypertension was present in 93 9 and Baer[115] in as high as 98 9 per cent of cases of cerebral hemorrhage not due to a local cause

rhage. However, there is another factor that is also present in practically all cases of cerebral hemorrhage, namely, arteriosclerosis of varying but most often very marked severity Apparently, however, cerebral arteriosclerosis *per se* very rarely leads to massive cerebral hemorrhage, for though one often encounters marked arteriosclerosis of the cerebral vessels in the absence of hypertension, the above figures show that practically all instances of sanguineous apoplexy occur in the presence of elevated blood pressure

Pathogenesis of Cerebral Hemorrhage in Hypertension. —The question of how the hypertension produces the hemorrhage has been extensively studied in recent years It has long been known that extremely high pressures are required to rupture intact arteries In an investigation on cadavers, Lampert and Mueller[116] found that even with pressures as high as 1,520 mm of mercury, they were able to rupture the cerebral vessels in only 2 of 30 cadavers, and both these were of syphilitic individuals In 10 cadavers of persons who had hypertension, these enormous pressures caused rupture in only 2 Such intravascular tensions, of course, are never en-

cerebral hemorrhage They believed the miliary aneurysms to be the consequence of diffuse periarteritis and not of arteriosclerosis of the cerebral vessels, for they found them in the absence of the latter This view was widely accepted until it was shown by Pick[118] and his pupil Ellis[119] that the so-called miliary aneurysms are not true aneurysms but false dissecting

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about them. The fatal hemorrhage occurred from the rupture

of arteriosclerotic vessels without aneurysms or from larger aneurysms; in fact, Pick was able to demonstrate by a special technique the actual rupture in no less than 8 of 11 cases. In an investigation of 107 fatal cases of cerebral hemorrhage, Zimmerman[120] found that—apart from 12 cases due to brain tumor, subacute bacterial endocarditis and blood dyscrasias—in 14 the extravasation resulted from rupture of a genuine saccular aneurysm of one of the larger vessels of the circle of Willis and in 80 from rupture of an intramural hematoma of a small intracerebral artery through the adventitia into the brain substance. Zimmerman's studies indicate that the intramural bleeding in the atheromatous arteries originates from the numerous thin-walled vasa vasorum present in the thickened walls

Rosenblath[121] made the observation that in the area immediately surrounding the massive hemorrhage, in which there are often multiple small hemorrhages, the small arteries have necrotic walls, and suggested that the necrosis of the arterial wall is the cause of the hemorrhage. This theory has been supported by Westphal,[28] who believes that the necrosis of the vessels is the result of angiospasm. The ischemia resulting from the spasm causes necrosis of arteries, capillaries, and veins, so that when the spasm relaxes the reentering blood ruptures the vessels. Westphal bases this theory on extensive clinical, pathological, and experimental studies. He observed various precursory clinical manifestations of cerebral hemorrhage which he interprets as angiospastic in origin In some of his cases of cerebral hemorrhage, in addition to the hemorrhagic area there were areas of white softening (encephalomalacia) for which vascular closures could not be demonstrated, so he considers them as manifestations of the prehemorrhagic angiospasm. Schwartz[122] also believes that cerebral hemorrhage in hypertension starts as a hemorrhagic infarction due to vasomotor phenomena in terminal arteries; the bleeding, according to this investigator, is by diapedesis, and the massive hemorrhages result from the confluence of smaller ones. Westphal's work has been severely criticized by Ruehl,[123] who believes that the changes in the vessel walls, apart from those secondary to the hemorrhage, are purely arteriosclerotic and not necrotic. In his opinion, the cause of the hemorrhage is the yielding of an atheromatous area in the vessel wall before the high blood pressure

Anatomic evidence that massive cerebral hemorrhage often occurs in a focus of previous softening is presented by Globus and Strauss[124] According to their conception, arteriosclerotic narrowing and closure of arteries result in the production of areas of softening which deprive the cerebral vessels of a certain amount of support, this loss of support they believe to be an important contributory factor in the rupture of an atheromatous vessel by the high intravascular tension. However, Cobb[125] points out, in opposition to the theory of Globus and Strauss, that the fluid and soft substance surrounds the vessel at a pressure practically as great as that of the normal tissue. For an exhaustive account of investigations on the pathogenesis of cerebral hemorrhage, the reader is referred to the

Precursory vascular spasm and infarction have been suggested as additional precipitating factors, but their significance has not been established.

the Occurrence of Cerebral Hemorrhage.—While, in

for years without resulting in apoplexy.

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Paroxysmal rises in arterial tension preceding cerebral hemorrhage have been described by Westphal[28] and others. All factors which produce sudden rises in blood pressure favor the occurrence of cerebral hemorrhage. Thus, an apoplectic seizure not rarely occurs during great excitement or straining at stool

rest or sleeping, po

blood pressure due to dreams as described

Fahrenkamp[10] and Westphal claim that cerebral hemorrhage is more frequent in those cases of essential hypertension in which there are great fluctuations in blood pressure than when the arterial tension is relatively

malacic process. In some instances, it appears like a thunderbolt from a clear sky, immediately proving fatal to an individual who was not aware that he had hypertension. In other cases the apoplectic stroke occurs only

of essential hypertension, for such recognition would incline one toward more intensive medical treatment or sympathectomy. Unfortunately, the likelihood of a stroke cannot always be prognosticated. However, in a careful study of the clinical picture of 19 patients with essential hyper-

or papilledema or exudates. Their patients developed their stroke 0.8 to 5 years after the appearance of the first of these symptoms.

An individual may have only one cerebral hemorrhage and then get

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that in such cases

, so that the chief danger is recurrence of the apoplexy. In other instances, there are several

or even many hemorrhages of varying severity. However, this is very exceptional. Many of the cases regarded as having had repeated major cerebral hemorrhages actually have had episodes of cerebral infarction due to thrombosis. It is worthy of reiteration that the mortality of massive cerebral hemorrhage is extremely high. Especially because of the surgical treatment that has apparently been life-saving in some cases, the differentiation between hemorrhage and thrombosis is important. For this the reader is referred to treatises on neurology; here it will only be mentioned that in the large majority of massive cerebral hemorrhages the spinal fluid is bloody.

Primary subarachnoid hemorrhage may complicate essential hypertension. But it is not nearly as closely correlated with hypertension as is intracerebral hemorrhage. Hypertension was present in 8 of 46 patients with primary subarachnoid hemorrhage studied by Wolff.[127] It is especially in older patients with subarachnoid hemorrhage that hypertension is apt to be found.

CEREBRAL ARTERIOSCLEROSIS IN ESSENTIAL HYPERTENSION

Cerebral arteriosclerosis, as has been mentioned, is found at necropsy in almost all cases of essential hypertension Very often, the disease of the cerebral arteries is severe enough to have well-marked deleterious consequences for the brain substance. In fact, it is unusual not to find on careful search some areas of softening in the brain of an individual who suffered from essential hypertension. Hypertension, however, does not play the dominant rôle in the production of encephalomalacia that it does in cerebral hemorrhage; thus, Zimmerman[120] found that while hypertension had been present in all of 42 fatal cases of cerebral hemorrhage, the blood pressure had been high in only 18 of 49 fatal instances of cerebral infarction.

In a not inconsiderable number of cases of essential hypertension, the consequencies of cerebral arteriosclerosis cause well-marked symptoms which may be the primary complaints of the patient Lack of space forbids detailed description of the variegated symptomatology of cerebral arteriosclerosis, for which the reader is referred to treatises on neurology It has already been mentioned that headache, vertigo, and other cerebral symptoms in essential hypertension are doubtless often manifestations of cerebral arteriosclerosis. Also discussed above was the "pseudoneurasthenic" picture of cerebral arteriosclerosis with such complaints as irritability, diminished capacity for work, impaired memory, weakness, loss of weight, insominia, headache, vertigo, etc., a variety of case which is often misinterpreted. But as the injury to the brain substance becomes more widespread, the origin of the symptoms becomes clear Appropriately located thrombotic occlusions with resultant foci of softening may lead to hemiplegia, monoplegia, aphasia, etc Widespread cortical injury may produce pseudobulbar palsy, or localization in the basal ganglia results in paralysis agitans or related syndromes There may be epileptiform seizures. Such patients form a considerable proportion of the inmates of chronic neurological wards. Finally, arteriosclerotic dementia

may develop; even the insane asylum receives its contingent of those whose troubles started with essential hypertension

THE KIDNEYS IN ESSENTIAL HYPERTENSION

... for the larger part of the cases ... From the conception the corollary was drawn ... at least largely due to defective renal function. This point of view led to serious mistakes in the treatment of essential hypertension, perhaps the worst of which, from the patient's point of view, was unnecessary dietary restriction extended over many years

It cannot be too strongly emphasized that *only a small proportion of individuals with essential hypertension suffer any serious symptoms or succumb as a result of damage to the function of the kidneys.* We have mentioned ... per cent of our cases of essential hypertension verified ...

hypertension which Paullin[128] observed for from five to seventeen years, only 1 died of renal failure Christian[129] found that of 131 deaths in patients with high blood pressure, 4 5 per cent were "renal deaths." Over 20 per cent of the deaths in Janeway's[1] series of hypertensive patients were due to uremia, but there were undoubtedly included instances of chronic glomerulonephritis, in which uremia is the most frequent cause of death

methods In most of the patients, renal injury later becomes evident, though in only the small minority just mentioned is it of lethal severity.

toms, careful examination unearths no evidence of renal disease The urine contains no protein and not even an Addis count discloses abnormal sediment The usual renal function tests—maximal specific gravity, phenolsulphonphthalein output, urea clearance, and blood urea and creatinin levels—yield a normal result. Likewise, measures of the individual processes in urine formation by the methods of the Smith school *may* disclose no abnormality *In some early cases of essential hypertension, renal blood flow, glomerular filtration, maximal tubular excretion of PAH, and maximal tubular reabsorption of glucose have been shown to be within normal limits* (Goldring[130] *et al*, Chesley and Chesley,[131] Goldring and Chasis,[132] Findley[133] *et al*, Corcoran[134] *et al*, Bolomey[135] *et al*, ...

relatively more than does the total systemic resistance. He showed that

this increase in renal resistance is largely due to rise in the resistance of the afferent arteriole, which may be *increased several fold;* Gomez considers that the slight increase in efferent and venular resistances may be in part a result of passive decrease in caliber consequent on lessened post-glomerular pressure. For a general discussion of renal hemodynamics in essential

As has already been seen, in essential hypertension biopsy specimens of the kidney may reveal no abnormality. Even at the necropsy of patients with essential *hypertension* who succumbed to cerebral hemorrhage or other nonrenal causes, the kidney may show no structural abnormalities or only arteriolosclerotic changes affecting small and widely separated areas of renal parenchyma.

Renal Damage in Essential Hypertension.—While essential hypertension thus starts *without clinically or anatomically demonstrable renal damage, the latter sooner or later becomes apparent in most cases.* Some patients have essential hypertension for a decade or more without even a trace of protein in the urine. In others, *injury to the kidney appears relatively early in the course of the disease.* Three mechanisms may damage the kidney in essential hypertension:

1. In one group of cases, postmortem examination of the kidneys reveals only arteriolosclerosis and arteriolosclerotic foci of atrophy such as also occur in almost all long standing cases of essential *hypertension,* even though *renal function during life was little affected. But these foci have* become so numerous and coalesced with one another to so great an extent, that there is left extremely little functioning parenchyma, apparently too little, despite the enormous factor of safety of the kidney, to maintain adequate excretion. I have seen a number of kidneys in which the very widespread but evidently purely arteriolosclerotic atrophy seemed adequate to explain the onset of uremia; in fact, one wondered how life had been maintained for a long time before the end with so little renal parenchyma. Such cases are usually encountered in older individuals, past the age of fifty and more often in the sixties. As a rule, the history and other evidence show that the hypertension has existed for many years. The progress of the damage to renal function is generally slow. The patient may be in the stage of compensated impairment of renal function with hyposthenuria but no azotemia for several years, especially if he is on a low protein diet. The concentration test may reveal the impairment of renal function while the urea clearance is still maintained at a tolerably good level by compensatory polyuria. And even after nitrogen retention has set in, the course may last for three, four or even more years. In these cases, contrary to those in the malignant phase described in the next group, the diastolic pressure is not necessarily very high and papilledema is absent.

2. In the second group of cases of essential hypertension that succumb
psy the lesions of the kidney
of the malignant phase of the
s and arteriolosclerotic atrophy,
there are arteriolar necrosis, endarteritis, often thromboses, and reactive

These cases usually occur in individuals who are

of the impairment of renal function is generally rapid ... of the diastolic pressure, retinopathy and often hematuria. In such cases of the malignant phase of essential hypertension, uremic symptoms may be the initial manifestations of the disease and bring the patient to the doctor. In others, on the contrary, the hypertension has been known to exist for years and is apparently running the usual course of essential hypertension, when a relatively sudden change for the worse comes, uremic symptoms appear, and examination of the renal function shows severe impairment. Such patients rarely live more than a year or two after the first detection of severe injury to renal function, uremia being almost always the cause of death.

3 In some hypertensive patients with renal arteriolosclerosis, heart failure and perhaps its treatment precipitate renal insufficiency and uremia.

clinical picture changes: the manifestations of congestive failure recede, but instead the patient complains of weakness, anorexia, loss of weight, nausea and vomiting, and finally becomes drowsy. Examination reveals evidences of dehydration, there are hyposthenuria and relative polyuria,

tion and mercurial diuresis are routine treatment for heart failure (*cf.* Fishberg[139]) As a result of such therapy, patients who in an earlier therapeutic era would have succumbed to congestive failure within a short period live much longer But in some of the cases renal insufficiency develops The latter may well be partly the result of the sodium restriction and mercurial diuresis, which diminish extracellular fluid and blood volume and consequently renal blood flow The latter precipitates failure of the already arteriolosclerotic kidney. It is possible, but not proved, that under

extent these changes are due to diminished blood flow, and how far to mercurial toxicity, remains to be determined

The manifestations of renal insufficiency and its resultant uremia in essential hypertension do not differ from those in other forms of kidney disease, and have been described in Chapters 2 and 7 Renal blood flow, glomerular filtration and such tubular functions as have been studied may fall to very low levels. Renal blood flow may be reduced to less than a tenth of the normal value in the final uremia. Glomerular filtration, as a

...he result that the filtration

.) The metabolic activities

... low levels, for Cargill and Hickam[140] found the

renal arterio-venous oxygen difference normal despite a greatly reduced blood flow.

THE URINE IN ESSENTIAL HYPERTENSION

In many patients with essential hypertension, the urine is in all respects normal—the volume corresponds to the fluid ingested, color and sediment are as usual, there are no abnormal constituents, and the normal bodies are present in appropriate concentration. In other cases, on the contrary, the urine reveals abnormalities.

Volume.—The volume of the urine is determined, apart from variations due to the quantity of fluid ingested, perspiration, etc., by the state of the heart and kidneys. With the appearance of cardiac weakness, the urinary volume diminishes. On the other hand, impairment of renal function is marked by an increase in the volume of urine, in an effort to compensate for the diminished concentrating power. Such patients may have an urinary volume of over 2000 cc. daily for years. In other cases, with appropriate dietary restriction, 1500 cc., or even less, may constitute a relative polyuria and compensate for even a severe diminution in [illegible] ting power. [illegible], for it usually [illegible] the impairment of renal function It is to be remembered that when the heart fails in a patient whose renal function is already severely impaired, the concentration of the urine cannot rise, so the only change is a diminution in volume.

Nocturia -Nocturia is a symptom of which many patients with essential hypertension complain. There may be only a relative increase in the volume of the night urine or else the absolute quantity of the latter may exceed that of the day urine (nycturia) The symptom may be due to either cardiac or renal insufficiency, the former being the more common in essential hypertension. When the nocturia is of cardiac origin, the concentrating power of the kidney is little impaired, and the urine has the usual characteristics seen in cardiac failure. In such cases, the increased volume of the night urine is due to the absorption of occult or manifest edema while the patient is in bed. On the other hand, when the nocturia is of renal origin, the patient is unable to concentrate the urine, which is pale and of low specific gravity Here, the reason for the nocturia is that the kidneys have to eliminate a large volume of urine at all times in order to compensate for the diminished concentrating power. If the nocturia is of renal origin the 24 hour urinary volume is increased, while the latter is decreased in the nocturia of heart failure. In all hypertensive males of advanced years who have nocturia, one should not fail to examine for prostatic disease, which is a fairly common accompaniment of essential hypertension.

Protein.—Protein may or may not be present in the urine in essential hypertension. Of 458 hypertensive patients studied by Janeway,[1] 144 did not have albuminuria. Many patients with essential hypertension have no proteinuria for years, while in others it is constantly present. Often the proteinuria is due to cardiac weakness and clears up as the circulation

such patients the systolic hypertension is apt to be more pronounced than the diastolic because of the usually high degree of aortic arteriosclerosis.

5. Diabetes and hypertension may both be manifestations of the Cushing syndrome. The association of diabetes and hypertension has also been observed in pheochromocytoma.

THE EYE IN ESSENTIAL HYPERTENSION

Changes in the fundus oculi are very common and often of great diagnostic and prognostic significance in essential hypertension. The following table summarizes the ophthalmoscopic findings in 189 patients with essential hypertension at Mount Sinai Hospital:

OPHTHALMOSCOPIC FINDINGS IN ESSENTIAL HYPERTENSION
(FISHBERG AND OPPENHEIMER[141])

			Renal Function		
				Impaired	
*Ophthalmoscopic observations**	*Number of Cases*	*Deaths in hospital*	*Unimpaired*	*Compensated*	*Decompensated*
Normal fundus	13	1	13	0	0
Contracted arteries	11	0	9	2	0
Retinal arteriosclerosis	70	9	57	11	2
Arteriosclerotic retinopathy	58	5	37	12	9
Hypertensive retinopathy	37	13	11	7	19

* In 32 of the 37 patients with hypertensive retinopathy, retinal arteriosclerosis was also present. The arteries were contracted in varying degree in all instances of hypertensive retinopathy and in most, if not all, of the arteriosclerotic fundi. The criteria of retinal arteriosclerosis, arteriosclerotic retinopathy and hypertensive retinopathy are summarized in Chapter 12

It should be borne in mind that the above statistics refer to hospital patients, in whom the incidence of severe retinal lesions is much higher than in private or dispensary practice.

A classification of the ophthalmoscopic changes similar to the above has been advanced by Keith, Wagener and Barker,[142] and has been widely used for the clinical grouping of cases of essential hypertension according to their severity and prognosis. The classification of the Mayo investigators is:

Group 1. Mild narrowing or sclerosis of the retinal arterioles.

Group 2. Moderate to marked sclerosis of the retinal arterioles, with exaggerated light reflex, arteriovenous compression, and irregular narrowing of the arterioles

Group 3. The above plus exudates, hemorrhages and retinal edema.

Group 4. The above plus measureable edema of the discs

Contracted Arteries.—The vast majority of patients with essential hypertension have narrowed retinal arteries. In fact, Gowers[143] long ago believed the narrowing of the arteries to be directly proportional to the elevation of the blood pressure. However, this does not always obtain, for one occasionally sees high blood pressure without obvious thinning of

the arterial
when not
being one
elevates th
usually in
tension an
ever, I have also been impr
constriction of the retinal arterioles, usually accompanied by tortuosity,
present in hypertensives in their 'teens, in whom the elevation of blood
pressure is as yet intermittent, who are asymptomatic, and who get along

O'Hare and Walker found definite retinal arteriosclerosis

sis (see page 382).

O'Hare and Walker pointed out that retinal arteriosclerosis is generally

vessels but with no evidences of present or antecedent hypertension, we found that sclerosis of the retinal vessels was absent or minimal, although there was often attenuation of the arterial blood columns On the other hand, O'Hare and Walker found that retinal arteriosclerosis is often present in individuals who previously had hypertension but whose blood pressure has fallen to within normal limits In such cases—in which the fall in pressure is generally the result of coronary artery disease—the retinal arteriosclerosis may be very valuable for the diagnosis of the antecedent hypertension

Hypertensive Retinopathy.—The appearance of hypertensive retinopathy in a patient with essential hypertension indicates that the disease has already passed into the malignant phase of the disease, and that necrosis

had necrosis of the renal arterioles On the other hand, arteriolar necrosis was not found at the necropsy of any of the hypertensive patients who did

no greater abnormality than a trace of protein, and blood was absent In such cases, in accord with the findings of Wagener and Keith (see

page 821), renal function was unimpaired. It appears very improbable that necrosis of the renal arterioles with its consequent severe lesions of the glomeruli should be present without more striking manifestations in the urine. In this variety of case, the onset of hematuria and other urinary changes may, it seems probable, document the onset of necrosis of the renal arterioles. Evidence that papilledema antedates renal arteriolar necrosis is afforded by renal biopsies taken at sympathectomy; in patients with papilledema arteriolar necrosis was not found (these were all cases with tolerably good kidney function). The clearing of hypertensive retinopathy is discussed below (p. 845).

Multiple small *hemorrhages* into the retina are not uncommon in hypertensive patients. Hemorrhages into other parts of the eye and occlusions of the central vessels are rare complications.

The prognostic significance of retinal lesions in essential hypertension is discussed on pages 380 and 844.

THE BLOOD IN ESSENTIAL HYPERTENSION

In many cases of essential hypertension, chemical, physical, and morphological examination of the blood reveals no abnormalities. In other instances, on the contrary, there are well-marked deviations from the normal, though none that are peculiar to the disease.

Chemical Properties.—As long as there is neither renal nor cardiac insufficiency, the non-protein nitrogen of the blood is within normal limits. Of the individual constituents of the non-protein nitrogen, urea, creatinin, amino-acids, and, as a rule, uric acid, are not increased under these circumstances. Occasionally, there is a modest increase in the uric acid content of the blood, up to about 5.5 mg. per cent. This has been found by Kylin,[145] Hitzenberger and Richter-Quittner,[146] and the author.[147] The cause of the increase of uric acid in these patients is not clear; none of my cases showed any clinical evidence of gout.

Nor are there any constant changes in such of the inorganic ions as have been studied—chloride, bicarbonate, phosphate, sulfate, potassium, sodium, calcium, etc. Since the flame photometer has made sodium and potassium determinations commonplace, it has been found that (contrary to older observations cited in the preceding edition) the ratios of plasma chloride, sodium, potassium and calcium to one another are undisturbed in uncomplicated essential hypertension Selye's[148] finding that the sodium/chloride ratio of the plasma increases with the severity of essential hypertension has not been evident in the extensive material at Beth Israel Hospital. Very great hypertension may be maintained despite low plasma sodium and chloride levels due to vomiting or other cause (*e. g*, 220/140 mm with plasma sodium 114 mEq. and chloride 78 mEq per liter.).

The acid-base equilibrium of the blood has been regarded as undisturbed in essential hypertension without renal or cardiac failure, the carbon dioxide combining power of the venous blood is within normal limits However, Waldron and Goldstein[149] have recently found that in patients with essential hypertension and normal blood urea, the hydrogen ion

the arterial blood
pattern of primary
... be a manifestation of pulmonary insufficiency

The cholesterol ... his studies with the tension have alrea... ultracentrifuge, Go... lipoproteins in the serum slightly elevated in hypertensives, but the difference is so small that it may be due to the inclusion in the hypertensive group of individuals with considerable atherosclerosis

there may be slight and usually fluctuating hyperglycemia, which, as a rule, shows no tendency to progressive elevation even though the patient's diet is unrestricted Blood sugar curves following the ingestion of glucose show that sugar tolerance is often, but by no means always, decreased (see O'Hare[151] and Musser and Wright[152]) The latter investigators find ...d diminished sugar tolerance is

...ormal limits, though Starlinger[153] found some tendency to hyperproteinemia as a result of slightly increased ...[54] also found the plasma ... with little change in the ... With cardiac failure, there is diminution in the albumin content of the plasma (Starlinger). Lewis and Page's[155] electrophoretic studies revealed little change in the plasma proteins in essential hypertension except in the malignant phase ...decrease in albumin and in-... experimental renal hyper-

With the onset of renal insufficiency, the characteristic changes in the chemical composition of the blood occur, they do not differ from those found in renal insufficiency due to other causes and have been described in Chapter 3

It may be remarked that cardiac insufficiency in essential hypertension, according to a number of observations that I have made, much more readily causes retention of urinary constituents in the blood than does cardiac failure due to valvular lesions One not uncommonly encounters well-marked increase in the non-protein nitrogen of the blood when the heart

non-protein nitrogen of the blood, which quickly clears up if the heart recovers.

Physical Properties.—It has been pointed out (page 293) that the total blood volume is normal in essential hypertension, unless there are complications. Likewise, the viscosity of the blood is increased in some of the cases (page 294), but in others it is within normal limits. Eckerstrom[158] has found that the colloid osmotic pressure of the blood is normal in essential hypertension.

While it seems to be established *that the plasma volume is unaltered in*

the extracellular fluid in the muscle of the hypertensive dog and Braun-

extracellular fluid volume *increased in both human* essential hypertension and experimental renal *hypertension. Contrariwise,* Gibbons and Chapman's[160] measurements *of the* thiosulfate space indicate normal extracellular *fluid volume in* essential hypertension; they also found total body water as measured by the antipyrine space normal in this disease. There is no *indication of striking* increase in extracellular fluid volume in the weight of *patients with uncomplicated* essential hypertension or in their response to mercurial diuretics; the possibility exists that the observations of increased extracellular fluid volume in essential hypertension may have concerned individuals with slight degrees of cardiac insufficiency.

The Blood Corpuscles.—In individuals with essential hypertension but no evidences of cardiac or renal insufficiency or severe arteriosclerosis, the red cells are usually *approximately* normal in number and hemoglobin content. It is true that there is a contingent of such individuals, decidedly in the *minority* in my experience, who have a moderate polycythemia. They *are generally* obese and often have a ruddy complexion, of the type popularly *considered as* "full-blooded." This group of plethoric-appearing hypertensive patients constituted the habitus *apoplecticus of older* clinicians, and actually have a high incidence of cerebral hemorrhage. But it *is to be remarked that* examination of the blood of such ruddy-complexioned *individuals by* no means always reveals an increase in the red cells or *hemoglobin*, and since it is known that they usually do not have an elevated blood volume, it *seems probable that the* plethoric appearance is largely the result of an altered distribution of blood This is particularly true of *women at the* time of the menopause with hypertension, whose flushed appearance is generally of vasomotor origin and who may be actually slightly anemic On the other hand, relatively pale individuals with hypertension *often prove* to have a normal blood count The influence of disturbances in vasomotor control in these patients is too great to enable one to foretell the blood status accurately from inspection That the blood volume is normal in essential hypertension, unless there is heart failure or another complication has already been seen (page 293).

ary anemia often appears and may be very marked. However, there are

many patients with both essential hypertension and severe cerebral arterio-
... whose clinical picture is dominated by repeated strokes and other

but ultimately these patients also usually become anemic. With congestive heart failure, there may be a high red cell count, but protracted cardiac insufficiency is usually accompanied by the development of secondary anemia.

Hemorrhages.—Hemorrhages are a striking feature in many cases of essential hypertension By far the most important form of hemorrhage in essential hypertension, cerebral hemorrhage, has been described above. We have also discussed the frequent retinal hemorrhages and the rare hemoptyses

In other cases, the epistaxis is from the septum The epistaxis may be very copious and difficult to control It is apt to recur repeatedly in the same patient, while other individuals with hypertension never have a nose-bleed

Menorrhagia and metrorrhagia are not strikingly more common in
docrine disease
eding is usually
necrosis in the

test is frequently positive in essential hypertension Soloff and Bello obtained a positive Rumpel-Leede phenomenon in 33 of 55 hypertensive patients, but there was no correlation with retinal hemorrhages. Hematuria is usually due to stone or other complication, but rarely results from arteriolar necrosis in the malignant phase Hematospermia may occur A very rare location of hemorrhage in essential hypertension is into the tympanum or other parts of the auditory apparatus (see Haug[166]). If the patient becomes uremic, there may be a hemorrhagic diathesis

It is a remarkable fact, which I am unable to explain, that the spontaneous hemorrhages of essential hypertension occur almost exclusively in the cephalic parts of the body—cerebral hemorrhage, retinal hemorrhage and epistaxis.

sis

in an individual with hypertensive and arteriosclerotic disease despite

what

[illegible] without noting increased susceptibility to hemorrhage; with cerebral thrombotic disease, contrary to some others, I do not use anticoagulants.

BASAL METABOLISM IN ESSENTIAL HYPERTENSION

aracteristic or constant

. The basal metabolism, also, is within normal limits in most cases of essential hypertension. It is true that Mannaberg[168] found an elevated basal metabolism in each of

of 170 cases of essential hypertension had a basal metabolism between +15 and −15 per cent. However, there are some instances of essential hypertension in which, despite the absence of myocardial insufficiency with dyspnea, the basal metabolism is elevated. The basal metabolism was between +15 and +20 per cent in 7.2 per cent and above +20 per cent in 3.4 per cent of the above-mentioned cases of essential hypertension studied by Boothby and Sandiford. In 827 hypertensives, Mountain[170] *et al.* found that the metabolic rate tends to increase with the blood pressure, but there were numerous individual discrepancies. Even in their Grade 4 hypertensives (classified by the retinal lesion, page 812), only 10 per cent had a metabolic rate above + 20 per cent. When the basal metabolic rate is elevated in a hypertensive, the possibility of pheochromocytoma, remote though it is, should be borne in mind. In my experience, *truly basal* readings of + 30 per cent or more in uncomplicated essential hypertension have been rare and almost always in patients with diastolic pressure exceeding 120 mm and entering the malignant phase. The cause of the acceleration of oxidative metabolism is not clear, sympathetic hyperactivity has been blamed (Rosenkrantz and Marshall[171]), but there is no supporting evidence Increased oxygen consumption of the hypertrophied heart and greater work by the respiratory muscles as a result of subclinical left ventricular insufficiency may be concerned. That the increased oxygen consumption in these cases is not due to hyperthyroidism is shown by failure of iodine, thiouracil derivatives or subtotal thyroidectomy to slow the metabolic rate. Mountain *et al* refer to cases in which anatomical examination of the resected gland failed to reveal the changes of hyperthyroidism, and I have seen the same. Determination of the protein-bound iodine in the serum and iodine uptake of the thyroid gland also show that increased basal metabolic rate in essential hypertension does not result from hyperthyroidism Studies of the creatine output in the urine by Treusch[172] *et al.* point in the same direction

A common situation is that in which the patient presents both diastolic hypertension and evidences of hyperthyroidism Such cases were long ago

("non-goitrous thyrotoxic
essure tachycardia"). The
the menopause. The chief

complaints are nervo
ness and loss of weight
neurotic. Apart from
enlargement, the mos
gland may or may not be enlarged.
perspiration. Exophthalmus is usually absent, but may be found. The basal metabolism is elevated and may even exceed +60 per cent.

At least the large majority of such patients have both essential hypertension and Graves' disease. This is often proved by radio-iodine studies

thyroidism has been present for years, but the reverse may also occur.

GENERAL APPEARANCE AND STATE OF NUTRITION IN ESSENTIAL HYPERTENSION

It has been seen (Chapter 25) that constitutional predisposition is probably a fundamental factor in the causation of most cases of essential

the predisposition of such persons to cerebral hemorrhage, the *habitus apoplecticus* of the older clinicians—has a very large element of truth in it. For "heavy-set" is descriptive of the sthenic habitus, obesity is very common in hypertensive patients, and there can be no doubt that a considerable proportion of hypertensive persons have ruddy complexions. The reason for the ruddy skin is evidently usually not plethora but an altered distribution of blood of vasomotor origin. In fact, Westphal[28] has shown that ectasis of the cutaneous capillaries is very commonly present in hypertensive patients. However, a minority of patients with essential hypertension do have increased blood volume.

Though the type just described constitutes a large proportion of the totality of patients with essential hypertension, and its presence may even be of some aid in the differential diagnosis between this condition and glomerulonephritis, it is to be emphasized that there are also individuals with essential hypertension who are *pale and thin*. Such pale and thin

sis
in an individual with hypertensive and arteriosclerotic disease despite what was regarded as adequate control of the prothrombin level. I have many times given anticoagulants to hypertensive patients with myocardial infarction without noting increased susceptibility to hemorrhage; with cerebral thrombotic disease, contrary to some others, I do not use anticoagulants

BASAL METABOLISM IN ESSENTIAL HYPERTENSION

It was seen in Chapter 25 that there is no characteristic or constant known metabolic anomaly in essential hypertension. The basal metabolism, also, is within normal limits in most cases of essential hypertension. It is true that Mannaberg[168] found an elevated basal metabolism in each of 20 patients with essential hypertension, but this is contrary to the findings of other workers. Thus, Boothby and Sandiford[169] found that 89.4 per cent of 170 cases of essential hypertension had a basal metabolism between +15 and −15 per cent However, there are some instances of essential hypertension in which, despite the absence of myocardial insufficiency with dyspnea, the basal metabolism is elevated. The basal metabolism was between +15 and +20 per cent in 7.2 per cent and above +20 per cent in 3.4 per cent of the above-mentioned cases of essential hypertension studied by Boothby and Sandiford. In 827 hypertensives, Mountain[170] *et al.* found that the metabolic rate tends to increase with the blood pressure, but there were numerous individual discrepancies. Even in their Grade 4 hypertensives (classified by the retinal lesion, page 812), only 10 per cent had a metabolic rate above + 20 per cent. When the basal metabolic rate is elevated in a hypertensive, the possibility of pheochromocytoma, remote though it is, should be borne in mind. In my experience, *truly basal* readings of + 30 per cent or more in uncomplicated essential hypertension have been rare and almost always in patients with diastolic pressure exceeding 120 mm. and entering the malignant phase The cause of the acceleration of oxidative metabolism is not clear, sympathetic hyperactivity has been blamed (Rosenkrantz and Marshall[171]), but there is no supporting evidence. Increased oxygen consumption of the hypertrophied heart and greater work by the respiratory muscles as a result of subclinical left ventricular insufficiency may be concerned. That the increased oxygen consumption in these cases is not due to hyperthyroidism is shown by failure of iodine, thiouracil derivatives or subtotal thyroidectomy to slow the metabolic rate. Mountain *et al.* refer to cases in which anatomical examination of the resected gland failed to reveal the changes of hyperthyroidism, and I have seen the same. Determination of the protein-bound iodine in the serum and iodine uptake of the thyroid gland also show that increased basal metabolic rate in essential hypertension does not result from hyperthyroidism Studies of the creatine output in the urine by Treusch[172] *et al.* point in the same direction

A common situation is that in which the patient presents both diastolic hypertension and evidences of hyperthyroidism Such cases were long ago

rom arteriolosclerosis, the frequent exhibition of mercurial diuretics may lamage the epithelial cells must be considered, but has not been proved.

2 It is with a second group of patients with essential hypertension who levelop renal insufficiency

Anatomical examination discloses, contrary to the first group, that the arteriolosclerotic atrophy of the kidneys is no more marked than one often sees in hypertensive patients whose kidneys were wholly adequate and who died of cardiac failure or cerebral hemorrhage. But in addition there are acute lesions of the small arteries—endarteritis, necrosis and thrombosis.

The differentiation of this second group of cases of essential hypertension ...vation of Volhard and ... its direct consequences, ... of instances of essential

sclerosis, and termed the condition the "combination form." However, Jores,[176] Loehlein[177] and others soon adduced evidence that these glomerular

for acute glomerulonephritis to occur in an individual with essential hypertension, but such a complication is apparently very rare. In view of these facts, Volhard and Fahr abandoned the conception of this type of

...ne arteriolosclerosis present in nearly all instances of essential hypertension, there are also other lesions of the arterioles. These consist in severe necrosis and endarteritis of the renal arterioles and are described in detail on page 683 Fahr applied the term *malignant sclerosis* to the cases in which arteriolar necrosis and endarteritis are present Similar cases were observed by Herxheimer[179] and Stern,[180] who termed them arterionecrosis. Fahr believed that ...

... but admitted that in others the etiology is totally unknown. Actually, there is no evidence that any of these etiological factors are operative.

These acutely progressive forms of hypertensive disease have been exhaustively studied by Keith, Wagener and Kernohan,[181] who have contributed importantly to our knowledge of the subject. They term the

In the presence of severe generalized arteriosclerosis the patient may become greatly emaciated and develop a brownish-yellow color of the skin so that he comes to [illegible] cachexia"). [illegible] tion. Often, nowadays, dietary restriction is the cause of great loss of weight. But in other cases of essential hypertension, and these are the more numerous, the patients do not lose weight, and the increasing obesity may be difficult to control.

THE MALIGNANT PHASE OF ESSENTIAL HYPERTENSION

In any of the diseases with diastolic hypertension—essential hypertension, glomerulonephritis, glomerulosclerosis, pyelonephritis, Cushing's syndrome, etc.—a characteristic clinical and anatomical syndrome may develop in the wake of a very high diastolic pressure: Severe headache, hypertensive retinopathy, renal insufficiency, manifestations of increased intracranial pressure, and at at necropsy acute necrosis, endarteritis and thrombosis of the small renal arteries. It will be seen below that these clinical and anatomical manifestations are the results of the high diastolic pressure, whatever the basis of the latter. The clinical picture is generally known as malignant hypertension If the underlying disease is known, as is usually the case, it may be more informatively, though less tersely, designated as the malignant phase of essential hypertension, the malignant phase of glomerulonephritis, etc.

Historical Development of the Concepts of Malignant Hypertension and the Malignant Phase of Essential Hypertension.—While in the large majority (over 90 per cent) of instances of essential hypertension renal function never becomes seriously impaired, in a smaller proportion the kidney does fail and the patients succumb to uremia. The clinical picture and anatomical findings reveal that such cases of essential hypertension with renal insufficiency are of two varieties:

1. In the first group the patient is almost always past fifty years of age. The diastolic pressure is generally not very high and may be no more than 100 mm. Papilledema is absent. The renal insufficiency is generally insidious in origin and often but slowly progressive. Necropsy reveals that arteriolosclerosis has obliterated so large a proportion of the renal parenchyma that the remaining part is quantitatively inadequate for excretion. The histological picture discloses a far-advanced stage of the arteriolosclerotic atrophy of the kidneys that develops in lesser degree in the large majority of patients with essential hypertension

This type of slowly progressive arteriolosclerotic renal insufficiency in older patients has become more common in recent years since rigid salt restriction and frequent mercurial diuresis have come into common use. Nowadays, many patients who formerly would have succumbed to heart failure live longer, but ultimately develop renal insufficiency It seems likely that decreased renal blood flow due to the two therapeutic measures mentioned may further damage the already arteriolosclerotic kidneys. The regressive changes in the tubular epithelium often present are perhaps of such pathogenesis. The possibility that, in a kidney already ischemic

will pursue divergent courses: some will remain almost asymptomatic,

and anatomical picture here termed the malignant phase of essential hypertension

It may be asked, with much reason, why it is necessary to introduce the term malignant phase of essential hypertension when no special appel-

tension is of special interest because it reveals the effects on the organism of protracted extreme elevation of blood pressure and is the clinical counterpart of the experiments in which maximal rise in arterial pressure and consequent arteriolar necrosis are produced by tight constriction of the renal

to damage
n the other
..ally cardiac
or cerebral—are almost always due to associated arteriosclerosis, which is not correlated directly with the height of the blood pressure From the practical standpoint, the recognition of the malignant phase of essential hypertension is most important because of the almost unconditionally ominous prognosis it carries.

Pathogenesis of the Malignant Phase of Essential Hypertension.—The characteristic features of the malignant phase of essential hypertension are due to the development of renal arteriolar necrosis and endarteritis, retinopathy and edema of the brain Why does a patient with essential hyper-

nant phase only after a protracted period of very high diastolic pressure. While the exact height and duration of the diastolic hypertension before the onset of the malignant phase vary in different individuals, most often the diastolic pressure has been above 130 mm at least a part of the time for a period of a year or more And in many of the patients the diastolic pressure exceeds 140 or 150 mm Moreover, while the diastolic pressure is not fixed in any individual, and may exhibit marked fluctuations even after the patient has developed papilledema or renal insufficiency, nevertheless in these cases the proportion of the time during which the diastolic

ic re-

... question is that of the mechanism through which the high diastolic pressure produces the arteriolar lesions, retinopathy and cerebral edema.

cases *malignant hypertension.* Keith and his coworkers emphasize the widespread involvement of the arterioles of the body which they found in various organs. They describe a type of retinitis which they consider characteristic of these cases (see page 373) and which they believe they can often differentiate from the retinitis that may occur in glomerulonephritis

It will be noted that these two commonly used terms, malignant sclerosis (or malignant nephrosclerosis) and malignant hypertension, designate different aspects of the same condition. Malignant sclerosis was coined by a pathological anatomist to connote an especially severe and rapidly progressive type of renal arteriolar lesion On the other hand, malignant hypertension was introduced by clinicians to designate a form of hypertension pursuing an especially rapid and severe clinical course. Unfortunately, the use of t
sclerosis has fostered a
sui generis, distinct fro
is shown by the following evidence:

1. In a high proportion of the cases, "malignant hypertension" appears after many years of known asymptomatic essential hypertension.

2 At post-mortem examination, in addition to the relatively recent changes of "malignant hypertension," the kidneys exhibit the long standing arteriolosclerosis, glomerular hyalinization and other lesions which are found in almost all cases of essential hypertension.

3 The family history of most patients with "malignant hypertension" reveals that other members of the family suffer from essential hypertension. I have repeatedly observed "malignant hypertension" in relatively young individuals both of whose parents had essential hypertension.

4. As mentioned above, the clinical picture of malignant hypertension (*cf.* Derow and Altschule[182]) and the post-mortem finding of renal arteriolar necrosis and endarteritis develop not only in essential hypertension but also, though much less often, in hypertension due to glomerulonephritis,

diastolic pressure, whatever its origin. Perera and Haelig[183] have pointed out that when hypertension results from unilateral kidney disease, it is especially apt to run a severe course and enter what is here termed the malignant phase My experience accords with this observation.

"Malignant hypertension" or "malignant nephrosclerosis" is thus most often no more than a designation for *one* of the several clinical and anatomical guises which essential hypertension may assume As will be seen in the following, in the large majority of instances what has been termed *malignant hypertension or malignant nephrosclerosis is essential hypertension in which persistent extreme elevation of the diastolic pressure produces acute damage to the arterioles, hypertensive retinopathy and edema of the brain.* The latter in turn entail a characteristic clinical picture with an ominous prognosis. For these reasons, we shall speak of the *malignant phase of essential hypertension* and thereby bring out that we are dealing, not with an independent disease, but with an ominous form of that very common disease, essential hypertension. A group of patients starting with essential hypertension

of one renal artery.

evidence is afforded by the experiments of Byrom and Dodson. They produced brief overdistention of the arteries of young adult rats by forceful injection of fluid. This resulted in focal necrosis of muscle in the small arteries, with selective involvement of the arcuate and interlobular arteries and afferent arterioles of the kidney. But if a renal artery was protected from the rise in intravascular pressure by traction, the arterial lesions did not develop in that kidney Byrom and Dodson believe that in these experiments overstretching causes necrosis and lysis of arterial muscle with subsequent seepage into the damaged muscle of plasma and blood and fibrinoid transformation.

have been

necropsy revealed arteriolar necrosis which was confined to the contralateral kidney and absent from the arterioles of the kidney which was

widespread—involving the contralateral kidney, gastrointestinal tract, pancreas, adrenals and other organs—but the arterioles of the kidney

arteriolar necrosis and
f essential hypertension
are consequences of the rise in diastolic pressure

Hypertensive Retinopathy and Edema of the Brain.—Hypertensive retinopathy appears in practically every patient with essential hypertension

11 and 12, where evidence is summarized that they are consequences of

the height and duration of the diastolic hypertension that they withstand before developing the arteriolar necrosis, retinal lesions and cerebral edema

Arteriolar Lesions.—On page 683 it was seen that the malignant phase of essential hypertension is characterized by acute and severe lesions of the arterioles of the kidneys and sometimes of other organs. These lesions consist in arteriolar necrosis, cellular intimal thickening ("endarteritis") and thrombosis. It seems probable that these necrotizing arteriolar lesions represent an intensification of the same process which is documented in almost all cases of essential hypertension by arteriolar sclerosis. The evidence is strong that the acute arteriolar lesions are direct consequences of the extremely and persistently high blood pressure. This conception is strongly fortified by the experiments of Goldblatt[165] and of Wilson and Pickering.[166] Goldblatt found in dogs that if the clamp around the renal artery is tightened to such a degree that the blood pressure rises to extreme heights, the animal develops necrosis
the body with resultant hemorrhage
In rabbits, Wilson and Pickering foun
intimal thickening of the type generally termed "endarteritis" in human pathology; they consider it possible that "this cellular intimal thickening is produced by organization of the acute fibrinoid necrosis." Both Goldblatt and Wilson and Pickering found the acute arteriolar lesions most pronounced along the alimentary tract; the pancreas, liver, spleen, eye and other parts were involved to a lesser degree The skeletal muscles and kidneys were not affected.

The distribution of these lesions differs from that in human essential hypertension in that the renal arterioles are not affected in the experiments, while they are by far the most severely damaged in humans. It is precisely this difference that points most strongly to the pathogenetic rôle of the increased intravascular pressure, for in the experimental animal the arterioles of the kidney are protected from the hypertension by the clamp around the renal artery. Wilson and Pickering found the severity and extent of the lesions closely related to the degree of the hypertension. Goldblatt found that the lesions affect the bronchial but not the pulmonary arterioles. These facts point definitely to the importance of the mechanical factor of high blood pressure in the production of the acute arteriolar lesions. Nevertheless, since Goldblatt observed the necrotizing lesions in the dog only in the presence of renal excretory insufficiency, he believes that humoral factors resulting from renal failure are concerned in their pathogenesis. The experiments of Winternitz[167] *et al.* and of Muirhead, Turner and Grollman[168] and their coworkers have led them to a similar view; the latter investigators observed arteriolar necrosis in bilaterally nephrectomized dogs even in the absence of hypertension and believe that high blood pressure plays no more than an aggravating rôle in the pathogenesis of renal arteriolar necrosis.

These observations notwithstanding, the writer believes that there is convincing evidence that necrosis of the renal arterioles and endarteritis of the small renal arteries in malignant hypertension are primarily the result of the high blood pressure and not of chemical changes in the blood. I have repeatedly observed that *necrosis of the renal arterioles may occur in the malignant phase of essential hypertension before there is azotemia.* Similarly, Fasciolo and Kramer[169] observed that in experimental hypertension arterial lesions may appear in the presence of normal blood urea.

ache usually becomes very severe and difficult to control. However, in the terminal uremic stages headache most often disappears. Headache may be continuous for days or even weeks at a time, or may be intermittent. As in other clinical variants of essential hypertension, headache often awakens the patient in the early morning hours and may subside after he is up and about. The headache is most often occipital or diffuse, but it may be localized in any part of the head. Quite commonly it extends down the back of the neck and may be accompanied by nuchal rigidity. Sometimes stiffness of the neck is an early complaint in patients who are [illegible] lignant phase and they may be treated for a primary [illegible]

the possibility must be weighed that the disease is entering [illegible]

[illegible] and vomiting. In other [illegible], mental torpor and other manifestations of hypertensive encephalopathy (Chapter 11) appear; these may be initial symptoms.

Headache in the malignant phase of essential hypertension has diverse [illegible]

1. Severe cerebral a[illegible] the cerebral arterioles, [illegible] very common. Large hemorrhages also occur but are not common. Rosenberg[18] found destructive cerebral lesions in 12 of 17 patients with malignant hypertension.

2. Edema of the brain develops in a high proportion of patients in the malignant phase of essential hypertension. Cerebral edema is probably much more frequent than has generally been realized, because it is most [illegible] s been practically always [illegible] have witnessed [illegible] essential hypertension is [illegible] acranial pressure; papil[illegible]ledema and high cerebrospinal fluid pressure [illegible] *a patient with essential* [illegible] reason for this is that, [illegible] pertension is a result of [illegible] ages of essential hypertension, apart from patients with right-sided heart failure, the intra-

[illegible]

malignant phase

that are the hallmarks of the malignant phase. One factor that is of great importance is relative youth of the patient at the time of onset of definite hypertension. The average of individuals in the malignant phase of essential hypertension is decidedly lower than the mean of patients with essential hypertension in all its forms. Keith, Wagener and Kernohan[161] found that most of their patients with "*malignant hypertension*" were between thirty-three and fifty-five years of age, but the youngest was only nine years. Fahr[179] noted that while 76 per cent of his cases of ordinary essential hypertension were over sixty years of age at the time of death, only 7.5 per cent of those in the malignant phase of the disease were above this age. Most of the cases that I have seen were in thier thirties or forties, but a very few were much younger and some older. One of the Mount Sinai cases, reported by Klemperer and Otani,[194] was only eight and a half years old. Craig has also reported a typical case (with necropsy) that succumbed at the age of eight years. I do not recall seeing essential hypertension enter the malignant phase in any individual over the age of seventy years. It may be that the greater elasticity of the aorta in younger patients favors a higher diastolic pressure and thus the development of the malignant syndrome. Another factor that seems to favor the development of the malignant phase is relativel [illegible] While in some patients with [illegible] first appears after a decade or [illegible] that definite hypertension has existed for less than two years In renal periarteritis nodosa and hypertension due to unilateral renal disease, in which marked hypertension may develop very rapidly, the malignant syndrome is relatively common. The same is true when the blood pressure rises rapidly in subacute or chronic glomerulonephritis.

Clinical Picture of the Malignant Phase of Essential Hypertension.—The characteristic symptoms of the malignant phase of essential hypertension are cerebral, renal and retinal in origin. In some instances these symptoms set in abruptly in an individual who was not aware of previous hypertension, though usually clinical (and almost always post-mortem) examination reveals that the blood pressure has been elevated for a considerable time In other cases the patient has been aware of hypertension, with or without symptoms but without impairment of renal function, for years. The malignant phase is usually ushered in by headache, less often by uremic symptoms, by convulsions or other manifestations of hypertensive encephalopathy, or by visual disturbances due to the retinal changes. The entire clinical course is rarely more than two years after the appearance of hypertensive neuro-retinopathy, the sign which proves to the clinician that essential hypertension has entered the malignant phase. Most often the patient succumbs to uremia, exceptionally to cerebral symptoms terminating in coma which are due to the increased intracranial pressure

Cerebral Symptoms.—Headache is, of course, a common symptom in all stages of essential hypertension. But it is most frequent and severe in the malignant phase. A patient rarely passes through the malignant phase without headache at one time or another Appearance, intensification or change in character of headache is the most common subjective manifestation of the transition into the malignant phase. Sooner or later, the head-

patients succumb to uremia, which usually progresses much more rapidly than in glomerulonephritis. As a rule, however, the headache and retinopathy ... the development of serious impairment of renal function ... the appear-

is entering the malignant phase. However, ... ceptions; on very rare occasions the lesions of the renal arterioles have progressed sufficiently to impair renal function notably before the optic disc becomes blurred. Comparing groups of patients in the malignant ... terminal glomerulonephritis, whose ... found that ... much lower ... tients in the

phase of essential hypertension arterial lesions in ... kidney play a large part Anemia is usually less extreme in the uremia of the malignant phase of essential hypertension than in glomerulonephritis. And while it is quite common for a patient with glomerulonephritis to ... is extremely rare in

may even be gross hematuria, though this is rare and always calls for consideration of the possibility of urolithiasis or another complication

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cranial pressure is not elevated. It is only when essential hypertension enters the malignant phase that the intracranial pressure rises and causes swelling of the disc.

The increased intracranial pressure due to edema of the brain is also revealed by *elevation in spinal fluid pressure.* The latter is most often between 250 and 350 mm. of water in patients with papilledema. Rarely, the spinal fluid pressure rises as high as 500 mm. of water; in the past, such cases have been confused with brain tumor. Schottstaedt and Sokolow[196] found the spinal fluid pressure elevated in 66 per cent and the spinal fluid protein content increased in 69 per cent of their patients with malignant hypertension. The increased spinal fluid pressure is not due to heart failure, for it may occur in the presence of normal venous pressure. On several occasions I have found that the increase in spinal fluid pressure antedates the appearance of papilledema in essential hypertension. The spinal fluid pressure often fluctuates widely within a day without obvious reason; under such circumstances, individual readings close to or even within the normal range may be obtained.

In some cases of essential hypertension in the malignant phase the consequences of the edema of the brain completely dominate the clinical picture, the manifestations of renal insufficiency are slight or even absent until the end. Under these circumstances the clinical picture closely simulates that of brain tumor: violent headache, vomiting, convulsive seizures, impairment of vision due to choked disk, stiffness of the neck, Babinski sign, high spinal fluid pressure, and ultimately coma not due to uremia. The patients may remain for weeks in a torpid or comatose state although azotemia is slight or absent. In such cases, disappearance of the headaches, improvement of vision and other salutary changes have followed decompression operations (page 363).

Hypertensive Retinopathy —This retinal change, described on page 368, appears sooner or later in practically every case. It is important to bear in mind that, of the retinal lesions that may appear in hypertensive patients, only hypertensive retinopathy reveals that the disease has entered the malignant phase, arteriosclerotic retinopathy, no matter how severe, has no diagnostic significance in this regard. Rarely, impairment of vision due to retinal lesions is the initial symptom, with the result that the patient first consults an ophthalmologist. The hemorrhages, white patches and papilledema of hypertensive retinopathy may appear in any sequence; ultimately, they are all mingled Hypertensive retinopathy usually, though not always, antedates pronounced impairment of renal function and sometimes even proteinuria. Especially biopsy observations at sympathectomy show that retinal lesions are usually far advanced before necrosis of the renal arterioles develops.

Symptoms of Renal Insufficiency.—The endarteritis and necrosis of the renal arterioles which characterize the malignant phase of essential hypertension lead to rapidly progressive impairment of renal function. As would be anticipated from the nature of the vascular lesions, the rate of deterioration of renal function is generally much more rapid than in chronic glomerulonephritis or pyelonephritis which have not been complicated by the malignant syndrome. The result is that the vast majority of the

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Chapter

27

ESSENTIAL HYPERTENSION: IV. DIAGNOSIS AND PROGNOSIS

THE DIAGNOSIS OF ESSENTIAL HYPERTENSION

THERE is usually little difficulty in establishing the diagnosis of essential hypertension, which is immediately indicated when a definitely abnormal elevation of systolic and diastolic pressure is discovered in the absence of inflammatory or obstructive disease of the urinary tract or endocrine disorder. The difficulties in interpreting the blood pressure in the broad border-land between the normal and abnormal have already been discussed (Chapter 8). Some of the circumstances in which differential diagnostic difficulties are encountered are the following:

1. Quite commonly, definite hypertension (*e. g.*, 160/100 mm. in a youth of eighteen years) is found in an insurance, military or other examination, and confirmed [illegible] t day yields norn [illegible] period are high. In such cases it is often impossible to decide whether the isolated elevated readings indicate that the individual will subsequently have sustained hypertension. Certain it is that the vast majority of such persons enjoy splendid health for many years thereafter and are better off not to know about the high readings. However, it is the experience of the writer that most of them ultimately are unveiled as having essential hypertension, although it may be decades before this is clear. In youthful subjects with intermittent elevation of blood pressure, the diagnosis of essential hypertension may be buttressed by a family history of hypertension, sthenic bodily habitus, and tortuous and narrowed retinal arterioles. Transient rises in arterial pressure under emotional stress are more indicative of future sustained hypertension if they are unaccompanied by tachycardia. It seems doubtful that the cold pressor and similar tests (page 764 [illegible] disease. [illegible] renal dise [illegible]

2. In women in whom the climacteric is accompanied by vasomotor perturbations, there may be transitory rises in blood pressure. In some of the cases the fluctuations in blood pressure disappear after months or a [illegible] of the climacteric rarely exceed 160/100 mm. The finding of constriction

or sclerosis of the retinal arterioles or of left ventricular hypertrophy may aid in establishing the diagnosis of essential hypertension.

3 During periods of protracted emotional tension, such as the depressed phase of a psychosis or combat duty (page 737), there may be sustained hy-

... in the malignant phase.

The clinical picture of severe hypertension, proteinuria, cylindruria, microscopic hematuria, renal insufficiency, retinal lesions, and no edema other than perhaps cardiac, may be present in either chronic glomerulonephritis

... high blood pressure antedated proteinuria shows that the hypertension is essential. Extreme hypertension, over 250 mm systolic and 150 mm. diastolic for more than a transitory period, is decidedly more common in essential hypertension, particularly in the malignant phase, than in glomerulonephritis though ... such ... tient

... one of chronic glomerulonephritis, for essential hypertension is rarely marked by proteinuria at this age. When the patient is in the thirties or forties, the differentiation may be impossible in cases presenting the features described above In the fifties and later, such a case is in all probability one of essential hypertension

5. The existence of essential hypertension may be masked by the effects of coronary arteriosclerosis. Myocardial infarction may lower very high blood pressure to normal or subnormal levels, and following recovery the blood pressure may not return to its previous level. And even in the absence of major infarction, coronary arteriosclerosis is sometimes accompanied by reduction of high blood pressure to normal levels. Such patients may remain with normal ...

... congestive ... paradoxically, they may be said to have essential hypertension sine hypertension. In such individuals, recognition of the disease essential hypertension may be difficult if there is no history of the antecedent high blood pressure ...

... hypertension has been present at some time. ... impairment of renal function, if disease of the urinary passages can be ruled out, speaks in the same direction. Sometimes, a rise in blood pressure as the heart improves reveals the essential hypertension

6. In patients with arterial hypertension and urinary obstruction resulting from prostatic enlargement, it may be difficult to decide whether the elevation of blood pressure is due to the urinary obstruction or to essential hypertension. The course of events after free urinary drainage has been established will settle the issue, though it is to be remembered that bed-rest can lower essential hypertension notably.

7. In patients with evidences of chronic pyelonephritis (of calculous or other origin), it may be difficult to decide whether elevation of blood pressure is due to the pyelonephritis or to independent essential hypertension. Impairment of renal function may be due to either, but good renal function speaks for essential hypertension. In long-standing atrophic pyelonephritis the urine may be grossly transparent and contain few leucocytes in the sediment. (*cf. also* page 649.)

8. The differentiation between essential hypertension and the chronic hypertension originating in the toxemia of pregnancy is discussed in Chapter 32.

9 On rare occasions hypertension resulting from unilateral kidney disease (pyelonephritis, perinephritis, obstruction of the renal artery, etc) is accompanied by practically normal urine produced by the other kidney and thus simulates essential hypertension The intravenous pyelogram is the first procedure in unveiling these cases.

10. Hypertension in the Cushing syndrome and pheochromocytoma may closely simulate essential hypertension. The differentiation is discussed in the sections on these diseases.

11. Hypertension due to renal polyarteritis nodosa may closely simulate essential hypertension. Because of the frequently rapid and extreme rise in blood pressure, renal polyarteritis may produce the picture of malignant hypertension with severe headache, hypertensive encephalopathy and hypertensive retinopathy. Usually, evidences of involvement of other organs, fever, eosinophilia and other manifestations of polyarteritis reveal the basis of the hypertension, and it may be confirmed by biopsy.

12 The purely systolic hypertension resulting from extreme arteriosclerosis of the aorta in the elderly, aortic regurgitation, heart block, patent ductus arteriosus, and Graves' disease should not be confused with essential hypertension.

13. Essential hypertension is common in diabetics It is to be differentiated from purely systolic hypertension due to aortic arteriosclerosis and renal hypertension in the Kimmelstiel-Wilson syndrome In the latter proteinuria usually antedates the hypertension but this is not always the case. The development of specific diabetic retinopathy (page 509) is especially helpful in the differentiation of the Kimmelstiel-Wilson syndrome It is to be borne in mind, however, that the hypertension of diabetic glomerulosclerosis may enter the malignant phase with papilledema and other changes of hypertensive retinopathy.

14. The hypertension of coarctation of the aorta is sometimes confused with essential hypertension. However, in coarctation the blood pressure is higher in the upper than the lower extremities, and usually no pulses can be felt in the feet.

THE PROGNOSIS OF ESSENTIAL HYPERTENSION

... hypertensive stage ...

... in which the blood pressure ...

stage extends back into childhood.

Little information is available, and that but incomplete, regarding the usual *clinical* duration of essential hypertension, *i e*, after high blood ... examination. There is, however, reason to

...

who "has never been to a doctor" is suddenly seized on the street and expires before the arrival of the ambulance, at necropsy, a coronary occlusion or cerebral hemorrhage is found, the association of which with hypertension is revealed by the presence of cardiac hypertrophy and renal arteriolosclerosis On the other hand, the hypertension may last for four or five decades and never do the subject any harm, until he finally dies of some disease having no relation to the hypertension

These pictures constitute the extremes, and the vast majority of instances of essential hypertension fill all conceivable intermediary gaps between them The person with elevated blood pressure is exposed to many dangers, and his expectation of life is distinctly shorter than if his blood pressure were normal This is well shown by insurance statistics May[1] gives the following figures of the Prudential Life Insurance Society, which show the mortality in 17,750 men and 2,500 women policyholders, 100 being the ratio of actual to expected deaths

Systolic pressure	*Mortality*
Not recorded	97 1
Under 140 mm	102 8
140 to 170 mm	133 6
Over 170 mm	219 6
Over 200 mm	827 5

with hypertension, are dead. It seems probable, however, that these figures give too short a duration of life for essential hypertension, for

Janeway's cases undoubtedly included instances of chronic glomerulonephritis, a disease in which the expectation of life is shorter than in essential hypertension. In a follow-up of 202 patients with systolic pressure above 175 mm., carried out from five to eleven and a half years after the elevation of pressure was detected, Blackford, Bowers and Baker[3] found that 50 per cent of the patients were dead; the male mortality was 70 per cent while 39 per cent of the females had succumbed. Ehrstroem[4] found that the average duration of life in essential hypertension is about ten years from the first subjective symptoms. He estimated that, on an average, hypertension has been present about ten years before the first symptoms, making a total average duration of about twenty years. More recently, Bechgaard[5] has reported a careful follow-up of 1038 patients whose blood pressure was higher than 180 mm. systolic or 160/100 mm. on their first visit to the Out-Patient Department. Four to eleven years later, he found that the mortality of the men was 272 per cent and of the women 143 per cent of that for the whole Danish population. As Bechgaard points out, this study tends to view the prognosis of essential hypertension in a favorable light, for the diagnosis was based on the initial reading, which is often the highest, and the control mortality rate for the whole Danish population includes those who were hypertensive. In a follow-up of ... and Groen[6] found the de... men and 91 per cent above the expected for women. Weitz[7] found that the maximum of the mortality ... less than f... with this, i. e., essential hypertension, on the average, cuts life short by about ten years.

Such documentations of the fact, brutally impressed on the busy practitioner almost every day, that essential hypertension curtails the life span, are of fundamental importance to the actuary. But they are of little help to the physician in the care of his patient. For the abbreviation of life by essential hypertension varies from nothing to decades, and what the practitioner needs is light on the prospect of the patient confronting him at the moment. This outlook is darkened by three general dangers:

1. *Direct Results of Hypertension.*—These include development of the malignant phase with retinopathy and massive cerebral hemorrhage. About 7 per cent of patients with essential hypertension enter the malignant phase, characterized by arteriolar necrosis, hypertensive retinopathy and cerebral edema—all of which have been seen to be direct consequences of high diastolic pressure (page 823). Massive cerebral hemorrhage is the more likely to strike the higher the pressure, but since necropsy shows that it occurs almost solely in patients with severe cerebral arteriosclerosis, the bleeding is apparently the result of both high intravascular pressure and arteriosclerosis.

2. *Arteriosclerosis.*—The symptoms of most patients with essential hypertension are due to arteriosclerosis in the heart, the brain and the kidneys in decreasing order of frequency. While hypertension undoubtedly accelerates the development of arteriosclerosis, it is not the primary cause. *The most important factor in the prognosis of a large majority of patients with*

sclerosis.

3. *Independent Disease.*—In a disease which stretches over decades, a high incidence of unrelated illness is inevitable. Thus, it is common to see patients with cancer in whom examination discloses essential hypertension, entirely unsuspected and which never influences the clinical picture. Perhaps a fifth of hypertensives succumb to entirely unrelated

a

has become more imperative than ever in recent years because the questio[illegible] so often arises whether or not sympathectomy or antihypertensive drugs are advisable or drastic dietary restriction called for. In the following some of the individual factors to be evaluated in estimates of prognosis will be discussed. Figures of duration of life in essential hypertension must, of necessity, vary with the type of patients included; those derived from life insurance or other routine examinations will show a longer expectation of life than those of a consulting internist, many of whose cases are seen only when severe symptoms are present.

Prognostic Significance of Sex.—The prognosis of essential hypertension [illegible]

age groups Another factor is that, for unexplained reasons, essential hypertension enters the malignant phase with high diastolic pressure and acute arterial lesions in a much smaller percentage of women than men.

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the co-existence of diabetes, the electrocardiographic findings, and the size of the heart—it is possible to obtain some estimate of the relative importance of the hypertension and the coronary arteriosclerosis in causing the heart failure. Generally speaking, and with many exceptions, the outlook is not as good when there are evidences of severe myocardial damage from coronary disease. But under all circumstances congestive failure is dangerous, and ultimately is the cause of death in over half the cases In rare instances a patient succumbs to pulmonary edema as a result of left ventricular failure, coming on either at rest or following exertion, without ever having been aware that he was hypertensive Most often, however, the first episode of congestive failure responds well to treatment and the patient may have a decade or more of useful life before [illegible] ...rial diuresis [illegible] failure that [illegible] Repeated

bouts of heart failure may respond well to treatment, particularly if [illegible] ...tion or medication, or especially overexertion, [illegible]

insufficiency Very many patients with essential hypertension [illegible] a stage of myocardial insufficiency in which therapeutic measures are no longer of any avail and they are bedridden most of the time, being able to [illegible]

After congestive failure has been long controlled by limitation of activity, salt restriction, mercurial diuretics and digitalis, evidences of renal insufficiency (weakness lassitude, drowsiness, anorexia, nausea, vomiting, [illegible]

poor, although sometimes repair of a sodium deficit leads to improvement [illegible] Con- [illegible] exist for years in hypertensive patients who are aware of no diminution in their exercise tolerance and are engaged in arduous occupations. Progressive enlargement of the left ventricle is evidence that cardiac insufficiency is becoming greater, and this is of course even more the case when the right

* A patient with hypertensive heart disease reported by Strade[18] lived for thirty-two years after his first episode of cardiac failure, at necropsy the heart weighed 875 Gm. and there was a pedunculated ball thrombus in the left auricle despite the absence of mitral stenosis I followed a patient with essential hypertension and coronary arteriosclerosis who had repeated bouts of failure during a period of over twenty years but was able to work between attacks until shortly before the end

gaard found that the excess mortality of his hypertensives under the age of forty was greater than that of the older hypertensives. Burgess[25] observed that the younger the age at which hypertension develops, the less likely is the patient to live out his full span of life. Hypertension which first becomes pronounced after the age of fifty, even when a true diastolic hypertension, most often pursues a mild course and may not shorten the patient's life. Of course, there are many exceptions to these statements; very marked hypertension starting in the thirties is, in exceptional instances, well borne for many years.

Prognostic Significance of the Height of the Blood Pressure.—The prognostic significance of the absolute height of the blood pressure is difficult to evaluate. In general, the prognosis is worse with a very high blood pressure (see the above figures of May), particularly a high diastolic pressure. The curve of mortality rises only gradually up to pressures of about 200/120 mm., but above these levels turns steeply upward. Nevertheless, it is not uncommon, especially in women, to see such pressures as 230/120 mm. well borne for years while the patient continues at his or her usual activities. When the systolic pressure exceeds 250 mm. or the diastolic is above 150 mm., the subject is always in danger, though even in such cases the patient may feel well for a considerable period. If the diastolic pressure exceeds 125 mm. in a high proportion of the readings, it is rarely more than two or three years before the disease enters the malignant phase. Not only is the development of the malignant phase more likely the higher the diastolic pressure, but there is also a correlation between the height of both the systolic and the diastolic pressures and the incidence of cerebral hemorrhage. However, while the incidence of malignant hypertension is linked only to the height of the diastolic pressure, cerebral hemorrhage often occurs when marked systolic hypertension is accompanied by only modest rise in diastolic pressure. Fahrenkamp[9] has found that in cases in which a curve constructed from several blood pressure readings daily shows marked remissions, the prognosis is decidedly better than when the pressure is fixed, even though the fixation level is somewhat lower than the highest oscillations in the first type of case. Those patients who react to bed-rest with a well-marked drop in blood pressure seem to do better than those whose pressure stays up despite mental and physical rest. Likewise, Stieglitz[10] finds the prognosis to be better in hypertensive patients in whom amyl nitrite produces a marked fall in blood pressure than in those without this reaction.

The purely systolic hypertension (*e. g.*, 190/80 mm.) of the elderly generally does not seem to affect the well-being of the patient. It is not a manifestation of essential hypertension, as the term is used here, but purely a result of the diminished elasticity of the arteriosclerotic aorta, and the dangers to the patient are those of arteriosclerosis alone.

Prognosis with Myocardial Insufficiency.—Congestive failure is always a matter for concern in essential hypertension. It is usually the resultant of the operation of two factors: hypertension and coronary arteriosclerosis. Very often—from consideration of a history of anginal manifestations or myocardial infarction, the circumstances in which failure developed, the height of the blood pressure, the presence of arteriosclerosis in other organs,

the outlook is serious, though in some such instances the patient ... ambulatory for several years, exceptic ... the possibility of sudden death in thes ... often of distinct aid in the prognosis. ... found that of "92 such patients w... myocardial involvement, 54 per cent died, and that within an average of eight months after the original electrocardiographic record was obtained. . . . On the other hand, of 49 more or less parallel clinical cases

... graphic changes who are able to pursue an occupation for a number of years ...

... hypertension and coronary ... response to therapeutic measures is generally not nearly so good as when there are no well-marked symptoms of coronary sclerosis.

Prognosis with Impaired Renal Function.—Impairment of renal function in essential hypertension is always to be viewed with concern. However, the tempo of progression of the renal damage varies widely, depending on the nature of the lesions in the kidney. From a prognostic, as well as a pathogenetic, point of view, three groups of cases may usefully be differentiated:

1. Cases in which the *impairment of renal function results from essential hypertension entering the malignant phase* The clinical picture of malignant hypertension has already been described ...

... the damage to renal function is due to acute arterial lesions—necrosis, endarteritis and thrombosis—and in the ...

... of renal function with hyposthenuria and poly-

ventricle enlarges. However, there are [illegible] ith marked [illegible] ow occupa- [illegible] for several years.

Diastolic *gallop rhythm* is a disquieting sign which indicates a high degree of impairment of the left ventricle; the rare systolic form seems to be of little prognostic significance. However, gallop rhythm may be only transitory, appearing during a paroxysm of cardiac asthma or a myocardial infarction, to disappear with improvement. Gallop rhythm often clears up as a result of treatment and the patient may then do well for years. A gallop that is elicited for only a few beats after exercise apparently indicates only a relatively slight degree of left ventricular insufficiency. White[16] found that 45 per cent of his patients with gallop rhythm died within two years.

Alternation of the pulse has long been attributed an exceedingly ominous prognostic significance. This undoubtedly holds for the well-marked form which can be recognized by simple palpation of the pulse; very few such patients live more than two years. However, even well-marked alternation may disappear as the patient improves under rest and medication, though the heart usually fails again within a comparatively short time. The slighter degrees of alternation, detected by the methods described above (page 783), have not nearly so serious a prognostic significance. While probably indicating severe myocardial strain or damage, they may disappear and the patient get along tolerably well for a protracted period. In the patients that I see, the pulsus alternans has become a rarity since the introduction of stringent dehydration.

The significance of the electrocardiographic pattern *of left ventricular strain* has already been discussed (page 771). There are many patients with this electrocardiographic change who get on well for five or even ten years and are able to be active. The strain pattern may disappear if the blood pressure falls as a result of sympathectomy or other treatment.

Prognosis with Angina Pectoris and Myocardial Infarction.—In hypertensive patients, the appearance of anginal pains due to coronary sclerosis or of myocardial infarction are quite as serious prognostic omens as in normotensives. It does not appear that the prognosis of coronary insufficiency and occlusion is altered notably by the presence of high blood pressure. A hypertensive patient may succumb to a myocardial infarction without having previously been aware that his blood pressure was high. Other hypertensives get along for many years with angina requiring frequent nitroglycerin tablets. One of O'Hare and Holden's[17] hypertensive patients lived for twenty-six years after her first severe attack of angina pectoris. Individuals with high blood pressure may survive two or even three major myocardial infarctions over a period of years. The capacity of the hypertensive for exercise is rarely as much after myocardial infarction. But sometimes, as with normotensives, the angina lessens. Following a coronary closure in a patient with hypertension, the blood pressure sometimes drops to normal or subnormal levels. If the blood pressure remains low, the outlook is generally very bad, though occasionally one meets such a case in which the patient is even able to attend to business for a few years.

the slow progression of the impairment of renal function in most cases with arteriosclerotic changes in the fundus is that the renal lesions are only arteriolosclerotic and necrosis and endarteritis are absent.

The ominous prognostic significance of *hypertensive retinopathy* has already been discussed. It shows that the hypertension has entered the malignant phase and in the spontaneous course of the disease most of the patients succumb within a year. However, in exceptional instances they survive two years or longer. I saw one patient in whom hypertensive retinopathy practically healed after being present for over a year, and the

which necropsy showed to be due to arteriolar necrosis. In the extremely large material of the Mayo Clinic, Keith and Wagener[29] observed in twenty years 15 cases of malignant hypertension in which papilledema receded; some of these lived a long time (1 survived one hundred and thirty-eight

Prognostic Significance of Other Symptoms.—The study of the proteinuria is usually not of any considerable prognostic aid. Essential hypertension may run its entire course and terminate in renal insuffiency with uremia, though there is but minimal proteinuria However, in relatively young patients with essential hypertension and no evidence of myocardial insufficiency, a high degree of proteinuria generally indicates a severe process in the kidneys, which sometimes, though not always,

hypertension not

, the blood sugar

is Heart failure is usually accompanied by increase in proteinuria, which lessens with

usually holds out well, they often deteriorate mentally and are always liable to cerebral vascular accidents

In evaluating the prognosis of hypertensive patients who have suffered a cerebral vascular accident, it is necessary to differentiate sharply between *cerebral hemorrhage and infarction*—and the distinction can generally be made The majority of patients who have suffered cerebral thrombosis with resultant infarction survive the episode, though with varying degrees of residual brain damage But *the mortality of intracerebral hemorrhage is extremely high* Statistics are difficult to obtain, but it has seemed to me that the large majority of hypertensives who suffer massive intracerebral hemorrhage succumb Moreover, they often die with appalling rapidity. Rose[23] found that 80 per cent of 205 cases of intracranial hemorrhage comm,

cases Of 116 fatal

cent d that 49 per

of spontaneous intracerebral hemorrhage, Zimmerman[24] found that 94 per cent succumbed in their first

uria in the absence of azotemia. Even after azotemia appears, the patient may get along quite well for several years. The azotemia sometimes diminishes as a result of high fluid intake with a high calorie-low protein diet. If heart failure has played a part in the renal decompensation, treatment of the heart may be followed by recession of azotemia.

3. Hypertensive patients with heart failure who have been treated intensively with salt restriction and mercurials not rarely develop renal insufficiency. The prognosis in these cases is serious, and while some of the patients improve as a result of administration of saline solutions, the majority succumb to uremia.

Prognostic Significance of Retinal Findings.—Ophthalmoscopic examination often yields data of great aid in the prognosis of essential hypertension. It may also be of notable help in deciding whether treatment with strong hypotensive drugs, sympathectomy or rigorous dietary restriction is indicated.

The table on page 812 affords an indication of the prognostic significance of the retinal findings. It is seen that patients admitted to the hospital with retinal arteriosclerosis and its consequences have a much greater mortality than those with normal or merely narrowed retinal arterioles, while the mortality is still higher by far in those with hypertensive retinopathy. Similar observations were made by Smith[12] *et al.* on 376 cases of essential hypertension which came to post-mortem. Using the Mayo classification of the retinal changes in hypertension (page 812), they found that of those in Group 1, 60 per cent succumbed to causes unrelated to hypertension and 3 per cent to uremia; Group 2, 35 per cent unrelated to hypertension and 2 per cent uremia; Group 3, 13.6 unrelated to hyperhypertension and 15.6 per cent uremia; and Group 4, 3 per cent unrelated to hypertension and 59 per cent uremia. Palmer[19] and his associates report the following mortality percentages in 430 cases of essential hypertension after 8 years: Group 1, 22; Group 2, 47; Group 3, 78, Group 4, 94.

The degree of *narrowing of the retinal arterioles* is not of great prognostic significance. It is true that with very high diastolic pressure narrowing is pronounced and in the malignant phase usually extreme. However, I have also often seen a high degree of constriction of the retinal arterioles in hypertensives in their 'teens who felt entirely well and got along well for at least many years after.

The presence of *retinal arteriosclerosis or arteriosclerotic retinopathy* indicates that the hypertension has been present for a considerable period. In accord with this, it can be seen from the table on page 812 that "the mortality and incidence of impairment of renal function in pateints with retinal arteriosclerosis are much higher than in those without retinal changes. On the other hand, they are much lower than in those with hypertensive neuro-retinopathy. Moreover, the rate of impairment of renal function in these patients is much slower than in those with hypertensive retinopathy. Individuals with essential hypertension and retinal arteriosclerosis or arteriosclerotic retinopathy may get on well for many years. However, most of the patients with severe arteriosclerotic retinopathy have evidence of arteriosclerotic disease in other organs, most often the heart or the brain, and their outlook is rather poor."[21] The reason for

came to necropsy at the Mayo Clinic, Smith[11] et al. found the following causes of death in per cent: congestive heart failure 26.1, coronary disease 9.8, cerebrovascular accident 14.9, uremia 20.2, and other causes 29.0. The ... is perhaps due to a higher proportion

... the percentage has been ... tion of salt restriction and mercurial diuresis (page 184).

It seems probable that if mortality statistics in hypertension included all with blood pressure above the normal, the percentage of those succumbing to causes having no relation to high tension would be much greater. For numerous patients are admitted to surgical, gynecological and other services who have elevated blood pressure but who have never had any symptoms of hypertensive disease and are thus omitted from statistics of causes of death in essential hypertension. Bell[14] states that "about three-fourths of persons with hypertension die of another disease." My experience is similar if the purely systolic hypertension of aortic arteriosclerosis is included.

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attack. It is all the more important to realize the very poor prognosis of spontaneous intracerebral hemorrhage since surgical treatment has begun to be used. Following survival of a cerebral infarction or hemorrhage, a patient with essential hypertension may live for many years, despite hemiplegia or other residua of the brain damage. However, there is always danger of another cerebral vascular accident. In these patients, also, the heart usually stands the strain of the hypertension very well, though there are exceptions in which coronary artery disease is the cause of death.

Diabetes mellitus and essential hypertension are a combination often compatible with many years of active life. The diabetes is usually mild or can be [illegible] re those of coronary or [illegible], or arteriosclerotic disease of the lower extremities.

Recovery from Essential Hypertension.—On rare occasions the writer has seen cases in which the blood pressure approximated 170/100 intermittently for a few years, and then had readings within normal limits for several years. But I have seen no patient with protracted hypertension as high as 200/120 mm. who became permanently normotensive. Following sympathectomy, the blood pressure may remain within normal limits [illegible] inal arterioles and [illegible] the disease is still operative. Protracted elevation of blood pressure during an anxiety state may return to normal after the emotional tension has been assuaged (page 737), but the relation of such elevation in blood pressure to essential hypertension remains to be established. Of course, the frequent cases in which an elevated blood pressure drops to normal because of cardiac failure are not to be considered as improved by the fall. To the writer it does not seem to have been demonstrated that essential hypertension is ever "cured."

Causes of Death in Essential Hypertension.—The chief dangers to be feared in essential hypertension are from the side of the heart and the brain, and not from the kidney as was thought during the period when essential hypertension was included in the concept of chronic interstitial nephritis. The most common causes of disability and death in essential hypertension are congestive failure and anginal syndromes, next to which in frequency are cerebral vascular accidents, particularly cerebral hemorrhage. Following these is the totality of the fortuitous complications that may occur during decade-long course of essential hypertension. Renal failure (*i. e.*, uremia) is the cause of death in only a small proportion of cases of essential hypertension. The statistics of Christian[11] and of Bell and Clawson[12] are representative of the general experience. The former found that of 131 patients with high blood pressure who succumbed while in the hospital, 32 per cent died of cardiac failure, 25 per cent of cerebral accident, 25 per cent of conditions independent of the hypertension, and only 4.5 per cent of uremia or with severe renal disease. Similarly, Bell and Clawson found that of 420 patients who died with essential hypertension, the cause of death was myocardial insufficiency in 187, coronary disease in 67, cerebral hemorrhage and thrombosis in 81, accident and intercurrent disease in 49, and renal insufficiency in 36. In 376 cases of essential hypertension which

get along very well for many years with little restriction and less treatment; they are not tormented by unnecessary prohibitions and useless therapy, as they so often were in the first decades after the introduction of the

the dangers of arterial hypertension. Almost everyone knows some unfortunate who had high blood pressure and died suddenly in the street, or is now paralyzed in half his body. Or when he tells his solicitous friends

cative friends who have had the dreaded high blood pressure for many years and "never been hurt by it."

It is very common nowadays for one who has always felt well to learn as a result of an insurance or periodic examination or a visit to the doctor for some trivial complaint that he or she has high blood pressure. Then, often enough, the peace of mind of the patient is gone, symptoms make their appearance, and there start the troubles of the patient and, even more, of the family. Iatrogenic symptoms are too often the principal

—At the al hyper- ithout it.

Many persons with asymptomatic hypertension would have been more fortunate if they had never learned of their hypertension. As things are, however, it is almost always necessary to tell an individual with hypertension that his blood pressure is elevated, for he is very apt to learn it from another source and then his confidence in the physician is destroyed. Or

of affairs, but cautioned against communicating the information to the patient

If possible, it is well to avoid telling the patient the exact height of the blood pressure, it is much better to tell him that the pressure is "somewhat" or "moderately" above that of most people. When the patient knows the height of the blood pressure, he is apt to follow it at every examination and be depressed when it is higher There are many patients with essential hypertension who follow their blood pressure as closely as

Chapter

28

ESSENTIAL HYPERTENSION: GENERAL MANAGEMENT AND DIET

ch [illegible]

are [illegible] and we can neither remove nor combat them. In many instances no methods at our disposal will serve to lower the blood pressure for any significant length of time without intolerable or dangerous side effects of the therapeutic procedure. In other cases, the arterial pressure can be lowered for at least a considerable period; sometimes the patient is benefited by this manometric success and sometimes he is not. When the blood pressure is lowered, however, we are merely treating the hypertension as a symptom, and the treatment is to be regarded as symptomatic and not the ideal causal therapeutics.

Ignorance of the causes of essential hypertension and inability to remove or alleviate them are not the only reasons for the often modest therapeutic accomplishments in this most common of serious illnesses. The major part of the suffering and mortality of hypertensive patients is not due directly to the high blood pressure but to arteriosclerosis in the heart, brain and other organs While hypertension accelerates the development of arteriosclerosis, it is not the basic cause. In those hypertensives in whom sympathectomy effects a marked reduction in blood pressure, coronary and cerebral arteriosclerosis continues to progress and the patients often develop myocardial infarction or cerebral vascular disease. Until means are developed to avert or retard arteriosclerosis, therapeutic results in the many individuals with both hypertension and arteriosclerosis will continue to leave much to be desired

Despite these basic therapeutic inadequacies, the physician can do a great deal for most hypertensives Without falling prey to self-deception, it can be stated that there have been considerable therapeutic advances in recent years. In some of the severe forms of essential hypertension—those advancing toward or in the malignant phase—dietary and pharmacologic treatment or sympathectomy may result in amelioration for worthwhile periods and prolongation of life The treatment of heart failure in essential hypertension—probably the commonest cause of incapacity in the disease—has been enormously improved in the past two decades There is no doubt that the hypertensive cardiac, on the average, lives much longer and more happily since the introduction of sodium restriction and mercurial diuretics. Another advance not to be underrated is the general, though unfortunately not universal, realization that most patients with essential hypertension

that are inevitable in everyone's life. An effort should be made to get them ... easily and face unpleasantness with equanimity. ... the patient

Regular hours should be kept, sufficient rest ... as far as possible. In the case of hurry of ...

women, family affairs are most ... inquired into and, if possible, ... women with hypertension, the p...

... believe, be done quite ... psycho-therapist, in fact, it would seem that the family physician ... his knowledge of the patient and his environment is best suited for the often arduous task.

The great importance of suggestion in the treatment of essential hypertension is strikingly illustrated by Ayman's[1] observations. He found ... hypertensive patients, seriously and en-

cent." ... hypertension as well as the spontaneous fluctuations in the blood pressure, that makes it so difficult to evaluate the actual specific effect of the innumerable remedies that have been suggested for the disease.

Mental and physical rest are often of great help to the hypertensive patient. In fact, it is probable that such success as is attained in health ... of treatment is in reality to be ... The influence of rest on ... the notably lower blood pressure in the morning. In the hospital, the highest blood pressure is usually found on admission, and it often declines very considerably as the patient stays in bed. In very many, though not all, cases of essential hypertension, it is found that if the patient is put to bed, his diet suitably restricted, and he is protected from excitement and worry, the blood pressure drops markedly. Sometimes it falls to normal levels, though this is exceptional. In other ca... hypertension in relatively yo... with severe arteriolosclerosis, ... pressure. The best results are obtained in those cases in which the blood pressure fluctuates considerably at different examinations even without bed-rest. Very marked diminution in the height of the blood pressure also often follows bed-rest in nervous individuals in whom worry, anxiety, etc., are accessory factors in elevating the arterial tension.

In order to obtain the best results from a "rest cure" in essential hypertension, as in other conditions for which the treatment is used, it is essential that the physical rest be accompanied by mental relaxation. Business worries, family troubles, etc., should be forgotten—an ideal which unfortunately cannot always be attained in practice. The necessity for mental calm must be borne in mind when ordering a man to leave his source of

at every office visit of the patient, so that he should not get an exaggerated idea of the importance of the absolute figures. Unfortunately, in many instances the patient insists on knowing the blood pressure, and it may have to be told him. I have often had this experience in the dispensary with illiterate patients; though they could not read, they wanted to know "how much blood pressure" they had that day.* In such cases, the true figures should be given, for if the pressure is understated, the patient may subsequently learn the true value and think he is rapidly getting worse. It should be remembered that many patients whose blood pressure is taken frequently learn to estimate the systolic pressure by watching the scale of the manometer and comparing the height of the mercury with the feeling in the arm or the first oscillations. All in all, the handling of many patients with essential hypertension demands a tactful physician, it is a task that is usually best carried out by the family physician who knows both the patient and his family.

[illegible] the regulation should not be too stringent. *Moderation in all things should be the watchword.* The application of this principle in the management of the hypertensive patient is discussed in the following sections.

Occupation.—Apart from extremely strenuous occupations, there are few callings that cannot be pursued by an individual with essential hypertension, as long as the heart is fully sufficient. It is by no means uncommon to encounter persons who have evidently had high blood pressure for years and nevertheless work as day laborers, masons, etc., without any trouble. Before advising a man to change an occupation which he has carried on without distress, one should, of course, always first ascertain if it is economically feasible for him to do so There is no use telling a man to discontinue his work when it is the only means of livelihood for himself and his family. This is often done without due circumspection, and the only result usually is that the person continues at his occupation but, in addition, worries over his blood pressure. In the case of women who keep house for a considerable family, it is often economically possible for them to lighten their labors considerably by the aid of other members of the family. It is also generally feasible to diminish the burdens of those whose occupation involves no great physical work but mental strain or long hours, notably business and professional men.

Mental and Physical Hygiene.—A great deal can often be done for the large contingent of individuals with essential hypertension who are "nervous," continually worrying and anxious over trivial unpleasant incidents

* A [illegible]
most a[illegible]
express[illegible] diabetic or the basal metabolism of an anxious woman who has been told she has Graves' disease They seem often to get much the same pleasure out of following the figures that they do from watching a horse race. Dr. H. A Derow tells me of a patient who bought herself a sphygmomanometer and stethoscope and took her blood pressure daily. Every effort must be made to avoid such close attention to the blood pressure.

The benefits of various forms of treatment of essential hypertension are ... the reassurance that goes with them.
... have undergone

Vacations.—The patient with essential hypertension ... ficient vacation. But before ordering a vacation, the physician should always be sure of the economic status of the patient, for no good purpose is served by advising a vacation to a person who cannot afford it. The ... vacation is taken is not

(such as those of the Rockies) to which they are not accustomed ... individuals with hypertension but no arterio-

fear of allowing hypertensive individuals to go to altitudes such as those of the Catskills or Adirondacks, where they usually feel well. This applies even to those who have recovered from a myocardial infarction or cerebrovascular accident. They ... voyages are often beneficial

... during the hot months, if this is feasible. However, most hypertensives who live in the northern states find the climate of southern Florida very satisfactory during the winter; especially those with symptoms of coronary artery disease are apt to be greatly benefited by a stay in the ... of respiratory ... or hypertensive ... and consequent pulmonary engorgement. Wherever the patient with essential hypertension takes his vacation, it should be made clear to him that he is going for a rest and not to participate in the manifold activities that make life in most summer resorts more

are not violent. Walking, golf and most types of fishing are well suited

livelihood or a woman her family to rest in bed; little will be gained by the physical rest if there is mental anguish. Usually, the maximum drop in blood pressure, if there is *any at all*, is obtained within a week or ten days, after which it stays at that level while the patient remains in bed. The use of drugs in combination with the rest treatment is discussed below.

Unfortunately, the blood pressure usually ascends to its previous level within a relatively short time after the patient returns to his occupation. For this reason, the indications for the rest treatment must be carefully evaluated before ordering it. There would seem to be no good reason for ordering bed-rest in an individual who is accidentally found to have high blood pressure but complains of no symptoms. On the other hand, in cases in which there are evidences of beginning myocardial insufficiency or such symptoms as great nervousness, headaches, dizziness, etc., a period of bed-rest will often produce great improvement which may persist for a long time or indefinitely after the blood pressure has returned to its previous level. In such cases, of course, better regulation of the patient's mode of life after leaving bed also plays a part in maintaining the improvement.

By action-potential measurements, Jacobson[41] has found that patients with essential hypertension have heightened contraction of the skeletal muscles. On this basis, he teaches hypertensive patients to cultivate daily habits of muscular relaxation and claims favorable therapeutic effects from this procedure. I have no experience with the treatment, which apparently requires protracted training.

Psychotherapy.—As a corollary of the psychosomatic theory of essential *hypertension*, increasing importance has been attributed in recent years to the psychotherapy of the disease. .
essential hypertension have been
Binger[43] *et al.*, Wolff and Wolf,[44] an [illegible]
original publications for details of their interesting observations. Wolff and Wolf conclude that "an interest by the physician in the feelings, attitudes, and life situations of patients with essential hypertension reduced or eliminated symptoms in about two-thirds. In a few, between one-tenth and one-fifth, the blood pressure was lowered to normotensive levels, for significantly, if not indefinitely long periods."

It was seen on page 741 that the available evidence does not indicate that emotional factors play more than a secondary rôle in the pathogenesis of at least the large majority of cases of essential hypertension. Nevertheless, in treating a hypertensive patient the physician should pay careful attention to the personality type, life situation and other psychologic desiderata. Such attention demands both considerable time and common sense—the latter of which, at least, all physicians will confess to having. If the physician can help to lighten the burden of domestic difficulties, business troubles, frustrated ambitions, suppressed resentment, etc., he will have accomplished a great deal for the patient—often more than he can do in any other way. Perhaps most important of all in the large majority of cases is reassurance. The mere diagnosis of high blood pressure conjures up visions of strokes and heart attacks in most people, and reassurance on this scare will often be rewarded by symptomatic improvement.

The benefits of various forms of treatment of essential hypertension are often largely due to the reassurance that goes with them.

In recent years, m[illegible] f hypertensive patients have undergone formal and deep psych[illegible]

purpose of helping the [illegible]

such psychoanalysis, with its great expen[illegible]

indicated other than for manifestations which would call for psychoanalysis even if the patient had a normal blood pressure.

Vacations.—The patient with essential hypertension should have sufficient vacation. But before ordering a vacation, the physician should always be sure of the economic status of the patient, for no good purpose is served by advising a vacation to a person who cannot afford it. The particular place where the annual or semi-annual vacation is taken is not of great moment, provided the climate is pleasant and the environment restful. The latter is the most important consideration. We have seen

pressure lowered to correspond to an altitude of 2000 meters, they react as do normals (page 267) with a drop in pressure. On the other hand, if the

ation if the heart is adequate. Most inland watering places are likewise suitable. Many patients with essential hypertension feel badly in hot weather, according to Kauffmann,[3] the blood pressure of most such patients rises in a hot room. They should leave for a cooler climate (as the mountains) during the hot months, if this is feasible. However, most hypertensives who live in the northern states find the climate of southern Florida

patients with left-sided failure and consequent pulmonary engorgement. Wherever the patient with essential hypertension takes his vacation, it should be made clear to him that he is going for a rest and not to participate in the manifold activities that make life in most summer resorts more

hypertension may con-

[illegible] exercise, provided the latter are not violent. Walking, golf and most types of fishing are well suited

to hypertensives. Young individuals with essential hypertension are not uncommonly athletic and desire to engage in competition. I have advised against this, but do not recall having seen acute pulmonary edema or other deleterious consequence definitely attributable to overexertion. In older patients who had previously been asymptomatic I have encountered both pulmonary edema and cerebral hemorrhage following overexertion; they doubtless had coronary or cerebral arteriosclerosis which had not become manifest. For this reason older patients with high blood pressure should avoid strenuous tennis, mountain climbing, rowing, swimming considerable distances, etc. The exercise prescribed in some of the gymnasiums that have become popular with business men in recent years is too vigorous for elderly hypertensives. If the patient is on a salt-poor diet, the possibility of ingesting considerable sodium chloride while swimming or bathing in the ocean should be borne in mind. With cardiac or coronary insufficiency, exercise should, of course, be appropriately curtailed. Patients usually exaggerate the importance of exercise in combating obesity; the amount of exercise a hypertensive can take is negligible in its effect on body weight in comparison to dietary restriction.

DIET

Ever since the clinical picture of what is now known as essential hypertension was recognized, dietetics has played a prominent therapeutic rôle. The diets have been either purely empirical or corollaries of the various metabolic theories of the disease, none of which have been sustained (Chapter 25) The regimens recommended for the disease have almost always been restrictive in nature. Few indeed are the foods that have escaped being blamed for high blood pressure, especially if they are expensive or enjoyable. Before the end of the nineteenth century protein restriction had come into vogue in the treatment of hypertension and in the first years of this century salt restriction was advocated It was quickly realized that caloric restriction is beneficial to at least obese hypertensives, and this was extrapolated to periods of almost complete starvation for hypertensives in general. Since the rôle of disturbances in lipid metabolism in the genesis of atherosclerosis has come to the fore, restriction of fatty foods has been advocated in hypertensives.

Protein Restriction.—Protein restriction has long been a popular measure in the treatment of essential hypertension, the origin of the procedure having been in the conception of essential hypertension as a primary disease of the kidney. Huchard[4] recommended the elimination of meat and fish from the diet because of his high estimate of the rôle of intestinal autointoxication in the causation of hypertension—an untenable hypothesis The supposed harm of proteins, particularly those of meat, in high blood pressure has been so widely inculcated into the laity that many individuals with hypertension have a phobia of meat and it is difficult to induce them to eat it. We have seen that there is no adequate evidence that excessive protein ingestion plays any part in the causation of essential hypertension and that the feeding of large amounts of protein to individuals with high blood pressure does not further elevate the arterial tension. Mosenthal[5]

that the blood pressure o

variations in the protein content of the diet. ... "feel better" when patients with essential hypertension state that they "feel better" when they abstain from meat, but this may be largely a psychic effect or an individual idiosyncrasy, for one often hears the same statement from persons with the most varied ailments. For some obscure reason, meat is the most feared of the protein foods in hypertension, while eggs usually escape condemnation and milk is often (*e. g.*, by Huchard) held in high esteem. Protein restriction is not rarely carried to such extremes in patients with essential hypertension that weakness, and apparently also anaemia, result, which disappear with the addition of protein to the diet. I have several times seen the nephrotic syndrome in individuals with essential hypertension and proteinuria in whom protein restriction had been ordered by the physician or more often adopted by the patient

tension. For this reason there seems to be no adequate justification for the rigid restriction of protein in the diet of the patient with essential

and the temperate use of other protein food. The question of the rôle of protein restriction in the rice diet is discussed below.

Restriction of Sodium Chloride.—Restriction of sodium chloride in the diet of hypertensive patients was recommended in 1904 by Ambard and Beaujard[8] Shortly after salt restriction had been introduced into the

time chloride was the element determined and gratuitously assumed to be significant) is accompanied by water retention and produces edema, while under other conditions salt alone is retained and hypertension produced. Ever since the observations of Ambard and Beaujard, the French have

their detailed communication of 1922, Allen and Sherrill reported on 180 severe cases of hypertension treated by salt restriction for periods of from one month to three years. In

was restored, in 41 9 per cent

while there was transitory bet

30 9 per cent. They found that cases with high plasma chloride did better under the treatment. Although "mild" cases showed a reduction in pressure while there were still several grams of sodium chloride in the daily urine, in 112 of the 180 patients the best results were obtained only when

less than 0.5 gram of chloride was excreted in the day's urine. Some of the cases required several months of the treatment, the longest being a year. Some time after, Volhard[10] also reported brilliant results from the salt-free diet.

The striking success reported by Allen and Sherill was not obtained by most other American investigators in the following years. McLester[11] and O'Hare and Walker[12] did not obtain better results with rigid salt restriction than with rest and moderate salt restriction. Mosenthal[13] did not find any influence of sodium chloride on blood pressure, the ingestion of so considerable a quantity as 10 grams of sodium chloride did not elevate the blood pressure in an individual with hypertension. Similar negative results were obtained by Berger and Fineberg[14] in a careful study in which they varied the sodium chloride content of the diet of hypertensive patients from less than 1 to over 30 grams daily. Rigid salt restriction was tried on a number of patients with essential hypertension at the Montefiore Ho [illegible]
anc [illegible]
the routing treatment.

As a result of observations such as these, the enthusiasm for salt restriction in hypertension originally awakened by Allen's studies was largely dissipated. By 1939 most clinicians, including the writer (*cf* Ed. 4 of this book), did not assess very highly the value of salt-poor diets in hypertension uncomplicated by renal or cardiac failure. But the fall in blood pressure which occurs in some patients on the rice diet revived interest in the relation of the salt intake to hypertension. It was shown that drinking salt water can produce hypertension in the rat (page 724). Grollman and Harrison[15] found that the blood pressure of hypertensive rats is lowered by abstracting sodium chloride from the diet; it remains low if potassium chloride is substituted but rises if sodium chloride is re-instituted. Grollman[16] and his associates studied 6 hypertensives on a 2000 calorie diet containing ample protein but less than 1 gram of sodium chloride. In 2 of the patients the blood pressure fell to normal, but rose again when salt was added; in at least 2 of the other patients salt restriction had no effect. Perera and Blood[17] found that rigid salt restriction (250 to 350 mg. Na) lowered the blood pressure of hypertensive patients, but the effect was not great Contrariwise, in another well-controlled series of hypertensives, Chasis[18] and his associates found that intensive salt privation (Kempner rice diet) produced no changes in the blood pressure of hypertensives greater [illegible]

diet. Bryant and Blecha,[19] Schroeder[20] *et al* and other investigators observed that some, but usually only a decided minority, of hypertensives have a lower blood pressure on a salt-poor diet Corcoran[21] *et al.* find that about one-quarter of patients with severe essential hypertension have a significant drop in blood pressure on a salt-poor diet My experience has been somewhat similar, though perhaps not as favorable. The results have varied widely in different types of cases. In patients with severe forms of essential hypertension first kept at rest with mild sedation for

about two weeks on an unrestricted diet, or after preliminary caloric restriction in the obese, I have found that subsequent institution of a rice or other very low (200 mg.) sodium diet produces further significant and *maintained* fall in blood pressure in only about 15 per cent of the cases. ... values. The

impairment of renal function or hypertensive retinopathy. By "maintained" is meant that the blood pressure does not rise as long as the sodium restriction is continued. In patients in the malignant phase with hyper- ... and/or severe impairment of renal function, the per-

under such circumstances it is difficult to rule out spontaneous fluctuations in the course of the disease Of course, low sodium intake often results in improvement in manifestations of heart failure and anginal symptoms even though the blood pressure is unaltered.

weeks to produce a response There are hypertensive patients in whom the blood pressure is first lowered when the sodium content of the diet is reduced to 200 mg And there are many cases—the large majority of the severe ones in my experience—in whom a maintained fall can not be achieved however low and long dietary sodium is reduced Finally, the writer would like to emphasize that there are very few patients with severe essential hypertension in whom salt restriction continues to keep the blood pressure at a significantly lower level for as long as two years

The frequently used "moderate" reduction of sodium chloride intake to

more often to 200 mg A diet containing less than 500 ...

of the kitchen of which most housewives are capable can be made tolerable

Many patients can pursue an occupation while on such a diet. But in some the temptation to stray is strong, and the physician is not rarely surprised by the results of sodium or chloride determinations on the urine of patients supposedly following a rigid diet.

The early French investigators attributed the hypotensive effect of salt restriction to the chloride ion. This assumption was doubtless due to the fact that at the time chloride and not sodium was measured. Later, when Blum showed that salt restriction clears edema through absence of sodium from the diet (page 160), the possibility became evident that the effects on blood pressure are likewise due to the cation. More recent studies point strongly in this direction. As mentioned above, Grollman and Harrison showed that restriction of sodium chloride decreases the blood pressure of hypertensive rats, but the addition of potassium chloride does not increase it. Addison[22] found that sodium and not potassium salts elevate the blood pressure of hypertensives previously on salt restriction. In patients with essential hypertension whose blood pressure had fallen on the rice diet, Dole[23] *et al.* found that ammonium chloride, contrary to sodium chloride, did not elevate the blood pressure. Strauss[24] observed that both sodium chloride and bicarbonate increase the blood pressure of women with toxemia of pregnancy. In diabetic children, McQuarrie[25] showed that sodium and potassium have antagonistic effects on blood pressure. The mechanism through which sodium restriction lowers blood pressure remains to be established. It may be correlated with the effect on water balance. Murphy,[26] Watkin[27] *et al.* and Chapman[28] showed that a low sodium diet (rice diet) diminishes the extracellular fluid volume (thiocyanate space). Murphy and Watkin and his associates also found evidence that the plasma volume is decreased. While a close correlation between the changes in plasma volume and the blood pressure has not been demonstrated, the possibility that the diminution in both the intercellular and plasma volumes may be an important factor in the clinical results of low sodium diets is worthy of further investigation. Whether or not the adrenal cortex is concerned in the hypotensive effect of sodium restriction is not established. Mendelowitz's[15] observations on digital vascular resistance after release of sympathetic nerve tone indicate that salt depletion diminishes intrinsic vascular resistance; this could, although the conception is no more than hypothetical, be due to lessened water content of the arteriolar walls.

Why sodium restriction lowers blood pressure in some patients with essential hypertension, and fails to do so in the majority of the severe ones and some of the mild ones, is not known. Since essential hypertension probably includes more than one entity, it is conceivable that sodium restriction is effective in only some of the diseases commingled in the concept of essential hypertension. Schroeder and his associates found an especially close relation between sodium intake and level of blood pressure in a group of obese female hypertensives having some, but not all, of the characteristics of Cushing's syndrome. However, in the classical Cushing's syndrome intensive sodium restriction has little effect on the blood pressure

Indications and Contraindications.—In recent years the virtues of low sodium diets have been so generally extolled that the majority of hypertensives are at least intermittently on them; patients take it for granted

in prescribing a diet

evidence available at present does not seem to justify the ... very low (less than 500 mg.) sodium diets for an asymptomatic hypertensive patient unless the diastolic pressure is threateningly high—say 125 mm or more For such asymptomatic hypertensives often get along very well for many years, and there appears to be no good reason why much of the joy of living and contributing should be taken away from them by a rigid diet in the absence of evidence that such restriction will postpone the onset of symptoms. In the presence of headache or other symptoms, or when the diastolic pressure exceeds 125 mm.—which experience shows is ... symptoms—sodium restriction should be

ment (apart from cardiac manifestations) be attained The attempt should be made to continue the sodium restriction indefinitely Most

sodium diets are trying, and in some who are supposed to be following such a diet examination of the chloride or sodium content of the urine discloses a higher salt intake In the large majority of patients in whom the blood pressure is lowered by sodium restriction, though not in all, the blood pressure rises again after months or a year or two even though they are punctilious in their adherence to the diet

Intensive salt restriction should be instituted only with the greatest circumspection in the presence of impairment of renal function Chasis,[18] Weston,[29] Watkin[27] and their respective associates showed that the rice

(except perhaps in some cases with heart failure), and only after careful consideration and with frequent controls of the blood urea when concentrating ability is impaired. With inability to concentrate the urine above a specific gravity of 1 015, the writer does not use very low-sodium diets. Failure to observe these restrictions has repeatedly precipitated uremia, sometimes fatal

Many patients can pursue an occupation while on such a diet. But in some the temptation to stray is strong and the physician is not rarely [illegible] e determinations on the urine [illegible] the hypotensive effect of salt restriction to the chloride ion. This assumption was doubtless due to the fact that at the time chloride and not sodium was measured. Later, when Blum showed that salt restriction clears edema through absence of sodium from the diet (page 160), the possibility became evident that the effects on blood pressure are likewise due to the cation. More recent studies point strongly in this direction. As mentioned [illegible] hypertensives previously on salt restriction. In patients with essential hypertension whose blood pressure had fallen on the rice diet, Dole[23] *et al.* found that ammonium chloride, contrary to sodium chloride, [illegible] observed that both sodium [illegible] ure of women with toxemia [illegible] children, McQuarrie[25] showed that sodium and potassium have antagonistic effects on blood pressure. The mechanism through which sodium restriction lowers blood pressure remains to be established. It may be correlated with the effect on water bal[illegible] Murphy,[26] [illegible] (rice diet) [illegible] Murphy an[illegible] volume is [illegible]. While a close correlation between the changes in plasma volume and the blood pressure has not been demonstrated, the possibility that the diminution in both the intercellular and plasma volumes may be an important factor in the clinical results of low sodium diets is worthy of further investigation. Whether or not the adrenal cortex is concerned in the hypotensive effect of sodium restriction is not established. Mendelowitz's[44] observations on digital vascular resistance after release of sympathetic nerve tone indicate that salt depletion diminishes intrinsic vascular resistance; this could, although the conception is no more than hypothetical, be due to lessened water content of the arteriolar walls.

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Indications and Contraindications.—In recent years the virtues of low sodium diets have been so generally extolled that the majority of hypertensives are at least intermittently on them; patients take it for granted

... and harmful intermediary products circulate, which

essing The rice is boiled or steamed in plain water or fruit juice, without salt, milk or fat. If the sodium concentration of the plain water available is greater than 20 mg per liter, distilled water should be used. All fruit juices and fruits are allowed, with the exception of nuts, dates, avocadoes and any dried or canned fruit or fruit derivatives to which substances other than white sugar have been added. Not more than one banana a day should be taken. White sugar and dextrose may be used *ad libitum*; on an average a patient takes about 100 Gm daily but, if necessary, as much as 500 Gm. daily should be used. Tomato and vegetable juices are not allowed Usually no water is given and the fluid intake is limited to 700 to 1,000 cc of fruit juice pre day." The diet is supplemented with vitamins. Since it is probably deficient in iron, this element should be given if the dietary restriction is protracted Kempner does not recommend rest in bed unless the severity of the condition necessitates it. As regards

salt or fat) may be added But only so much additional food should be allowed as can be ta ... blood pressure, heart size, ... rogen, etc. When a critical ... strict rice diet should be continued indefinitely provided that the equilibrium between the intake and loss of those substances which are indispensable for the body is maintained "

With enough sugar, Kempner's diet yields 2000 calories daily. It contains about 20 grams of protein and 5 of fat, with no cholesterol The diet is an extremely efficient form of salt restriction, containing only about 150 mg. of sodium and 200 mg of chloride in the day's ration The potassium content is of the order of 3 grams daily The patients generally lose weight during the first weeks While some of this is loss of water due to low-sodium intake, there is also tissue breakdown; often the patient is unable t ...
nance
at a lov ... but some of the patients who are zealous in their adherence reach a state of emaciation.

The 20 grams of protein contained in the rice diet is less than is generally believed to be needed to maintain nitrogen equilibrium. Nevertheless, Kempner maintains that patients can be kept in nitrogen balance on the rice diet because of the protein-sparing action of the high carbohydrate

Attempts have been made to reinforce sodium restriction in the treatment of essential hypertension by the use of mercurial diuretics (Megibow[30] *et al.*) or cation exchange resins. Gill and Duncan[31] treated 38 hypertensive patients for from four to ten months with diets containing 1 to 3 gm. of sodium daily and cation exchange resins. They believe that with the resins diets containing 1 to 1.25 gm. of sodium daily can be substituted for those containing only 0.2 to 0.5 gm. daily, with great increase in palatability. However, few patients feel that the slightly higher salt intake atones for the unpleasantness of the resins and many can not take the latter at all. In the absence of heart failure, I have not seen definite help from either mercurial diuretics or cation exchange resins and they are rarely long continued.

Caloric Restriction.—Obesity is very common in patients with essential hypertension. We have already discussed the deleterious consequences of obesity for the hypertensive patient, whose heart then labors under the double burden of the hypertension and the obesity During both World Wars it was observed that the incidence of hypertension is less during *periods of undernutrition (page 718). The possibility exists, though it is far* from proved, that a low lipid intake may retard the development of the arteriosclerosis that is the chief menace of the hypertensive patient. From various points of view, therefore, weight reduction is indicated in obese patients with essential hypertension Most often, diminution in the excessive body weight is not accompanied by more than slight reduction in blood pressure, but the fall is occasionally notable and rarely striking. Even though the hypertension is not lessened, the patient is often subjectively improved, dyspnea, in particular, may be ameliorated

The significant means of diminishing obesity in hypertensive patients, as in others, is reduction in caloric intake While moderate exercise is permissible and even desirable when the heart is fully competent, this is of little importance in reducing body weight in comparison to dietary limitation. If dexedrine is of help in reducing weight, the hypertension is not a contraindication, the combination with a barbiturate is usually advantageous in a hypertensive Thyroid extract is not indicated or helpful unless there is hypothyroidism. There are many hypertensives, notably those with features simulating the Cushing syndrome, in whom weight reduction is extremely difficult.

Fluid Restriction.—Water intak[illegible] mended in hypertension. We have of Miller and Williams that drinkin[illegible] may cause a transitory increase in the blood pressure of hypertensives. But there is no evidence that the ingestion of ordinary volumes of fluid is in any way detrimental in essential hypertension and no reason for restricting the fluid intake.

Kempner's Rice Diet.—A great upsurge in interest in the dietary treatment of essential hypertension and other hypertensive diseases was inaugurated by Kempner's[32] introduction of his rice-fruit-sugar diet. The rationale of the diet seems to have been the conception that a "renal metabolic dysfunction" exists in hypertensive diseases, as a result of which the metabolic processes of the kidney cells do not go on to the same end

Kempner found that the rice diet produced improvement in 322 of 500 hypertensive patients, as indicated by one of the following criteria: decrease in mean arterial pressure of 20 mm. or more, diminution of at least 18 per cent in the transverse diameter of the heart, inverted T_1 becoming upright, or disappearance of retinopathy. In 125 of 500 patients the blood pressure fell to 145/95 mm. or less. The length of time required for the blood pressure to decrease varied from four days to ten months. Very striking is Kempner's finding that papilledema disappeared in 17 of 23 patients who had this ominous finding.

A number of other clinicians have reported on their experiences with the Kempner diet (*cf.* Chapman and Gibbons[14] for a summary of the earliest studies, some of which were not well controlled) Chasis, Goldring[15] *et al.* carried out a carefully controlled study on 12 hospital patients with essential hypertension who were placed on the rice diet after a pre-treatment period of fourteen to seventy-nine days. Their conclusion was that the changes in blood pressure on the rice diet did not exceed those that might be anticipated as a result of random, spontaneous variations. An Out-Patient study by Loofbourow[16] *et al.* indicated benefit from the rice diet in 9 of 47 hypertensives Chapman followed 8 patients with moderately severe essential hypertension, headache and other incapacitating symptoms, but no evidences of renal insufficiency. They were put on the rice diet

and carefully controlled investigation of the rice diet with which the writer is acquainted Their 50 hospital patients with essential hypertension were put on the rice diet for a mean period of 10 5 weeks after a control period of 10 1 weeks They found that the basal systolic pressure fell in 46 of the 50 patients, with a decline of 30 mm. or more in 26, the basal diastolic pressure fell in 46 of the patients, the decline exceeding 20 mm in 13. Their "results in the relatively short period of observation on the rice diet

blood pressure and improvement in retinal and cardiac manifestations in 5 of 6 patients with essential hypertension who were kept on the rice diet for six months in the Metabolic Ward at the Rockefeller Institute However, even under these remarkably favorable conditions, which could hardly be duplicated for many patients, the final diastolic pressures were 90, 114, 92, 127, 84 and 106 mm.

In New York City, in recent years, a high proportion of hypertensive patients have been kept on the rice diet for longer or shorter—usually shorter and intermittent—periods The writer has thus had much opportunity to see the results of this dietary regimen, not only in his own patients but also in those treated by others The following impressions based on these observations in metropolitan practice may be of interest, since they were obtained under conditions akin to those in which the vast majority of patients must be treated.

intake. This view is supported by the observations of his coworkers, Peschel and Peschel,[33] who found nitrogen equilibrium in 11 patients who were on the rice diet for an average of eighty-nine days. Contrariwise, Schwartz and Merlis[34] found that patients on the rice diet are in negative nitrogen balance. The careful studies of Watkin[27] *et al.* likewise indicate that it is unlikely that nitrogen equilibrium is attained often on the unmodified rice diet; they point out that the bulky stools may contain considerable nitrogen. Chapman[28] also found that while the fall in weight in the early stages of the Kempner diet is due to loss of extracellular fluid and fat, later there is probably significant loss of active body tissue. Dole[23] and his associates demonstrated a gradual adaptation to the low-protein intake and, although their largest patients still had a negative nitrogen balance after three to five months of the rice diet, believe that ultimately equilibrium would have been attained.

As a rule the nonprotein nitrogen and urea levels in the serum change little on the rice diet and may even decrease because of the low-protein intake. An exception is constituted by some patients with impaired renal function, in whom the sodium privation may precipitate azotemia. As regards the serum electrolytes, Peschel and Lohmann-Peschel[35] found that after fifteen weeks on the rice diet, sodium, total base and pH were on the

when the initial cholesterol concentration was high. Starke[36] found that the decrease involved both the free and esterified cholesterol The possibility that the fall in serum cholesterol is not entirely due to diminished intake but may be at least partly the result of damage to liver function on the rice diet is indicated by the findings of Watkin *et al.* and Myers and Murphy[37] that the ratio of esterified to total cholesterol decreases and that the bromsulfalein, thymol turbidity and other tests often suggest impairment of liver function. The plasma protein levels most often are little changed. The same is true of the blood sugar; both Kempner and Watkin *et al.* found that the sugar tolerance of diabetics sometimes improves on the rice diet.

The evidence at hand indicates that when the rice diet lowers the blood pressure, it does so predominantly, if not exclusively, through the intermediacy of sodium restriction. In patients whose blood pressure has been lowered on the rice diet, addition of protein does not elevate the blood pressure (Chapman, own observations with Lonolac). It was seen above that results similar to those of the rice diet are obtained with low-sodium diets containing ample protein. That the hypotensive effect of sodium chloride restriction, when it occurs, is due to the sodium and not the chloride deficiency was also seen (page 858).

Results of the Rice Diet.—Comparative evaluation of the value of the [illegible] is handicapped by the difficulty of setting up adequate controls

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1. Some patients with severe essential hypertension whose blood pressure does not fall significantly on hospitalization, bed rest, mild sedation, and the usual hospital diet or weight reduction in the obese, have a statistically significant drop in blood pressure on the Kempner diet which is maintained as long as they stay on the diet. In these patients there may be relief of headache, dyspnea and other symptoms, the size of the heart may diminish and the electrocardiographic pattern of left ventricular strain improve, and rarely hypertensive retinopathy recedes. In the experience of the writer such a favorable response to the rice diet has occurred and been maintained in less than 20 per cent of patients who have not improved significantly on a preliminary control period of two weeks hospitalization with the usual mild sedation or weight reduction in the obese. The proportion of patients in the malignant phase in whom the rice diet has produced more than transitory improvement has been very small in my experience. In mild essential hypertension a high proportion of the cases react favorably to the rice diet, but such patients usually have already improved during the preliminary control period.

2. Symptoms of heart failure of course often improve rapidly on the rice diet—though no more rapidly than on any other form of low-sodium diet.

3. Few patients remain on the unmodified rice diet for long periods of time. To some the food becomes so repugnant after a week or two that they refuse to continue. Others are unable to consume their full quota of rice, fruit and sugar and lose weight rapidly. Many complain of weakness. In the experience of the writer, additions to the diet are required within a few weeks in the vast majority of instances whether or not improvement has occurred. Very few can pursue even a light occupation while on a rice diet with only slight additions.

4. In the observations of the writer there has been no difference in the results attained by very low-sodium diets (200 mg Na) and the rice diet. Comparison of the publications of Allen on the low-salt diet and Kempner on his rice diet indicates that both obtained similar results. It has been seen above (page 862) that available evidence indicates that when blood pressure is lowered by the rice diet, it is at least predominantly due to the sodium restriction.

5 The rice diet is unnecessarily restrictive There seems to be no good reason for limitation of protein; as seen above, addition of protein to the diet has been found by several observers and the writer not to affect the blood pressure There would seem to be no reason why the food should not be seasoned with spices, garlic, onions, vinegar, etc Nor should Neocurtosal, Diasal, ammonium chloride, potassium chloride, or other salt substitutes be denied to those who enjoy them As cited above, addition of ammonium chloride does not raise the blood pressure of patients whose tension has fallen on the rice diet. Limitation of water intake seems to have no rationale. That the restriction of lipids has a salutary effect on the hypertension or retards the development of arteriosclerosis remains to be demonstrated.

6. In those cases in which the blood pressure is lowered by the rice diet, the improvement lasts only as long as the diet is continued and by no means always that long. For this reason the rice diet should not be used

in those with

7 The rice diet should not be used ... does not seem to be wholly ... 55 per ... 77 mg.

per cent) developed "a m ... months on the rice diet." ... ever, be prescribed where impairm ... is no azotemia, is marked by inabil ... gravity above about 1.015. Under ... with the result that a low-sodium

fat, and affords a modest amount of protein as well as considerable energy from carbohydrate That the protein of rice, in conjunction with what little protein is obtained from fruit, is better adapted to serve as the sole source of protein than that of many other foods is not demonstrated It is worthy of consideration ... rice and fruit proteins may ... by Dole *et al* 250 grams of ...

often purely systolic hypertension following the regimen. The consequence has been that many individuals who should have years of well-being and useful accomplishment subject themselves to a very trying ordeal which takes most of the pleasure out of life and often transforms them—

General Discussion.—Kempner's introduction of the rice diet performed the valuable service of reviving interest in the dietary treatment of hypertensive disease, which had largely languished after Allen's work. Observations of patients on the rice diet has also contributed to understanding of the physiology of low-sodium, low-protein and low-lipid diets. Of special interest at the present time is the clear-cut evidence presented by patients on the rice diet that, despite the synthesis of cholesterol in the organism, the plasma cholesterol level can be lowered by limitation of lipid intake.

The therapeutic advantages and disadvantages of the rice diet are not yet unequivocally delimited. The blood pressure of some hypertensive patients falls on the rice diet. In my experience, however, a significant fall in blood pressure specifically attributable to the rice diet occurs in substantially less than one-quarter of patients with severe essential hypertension. Moreover, the rice diet has the following disadvantages: *it is miserably monotonous and unappetizing; many patients are unable to continue on the diet either for psychological reasons or because of continuing loss of weight and strength; apart from certain types of neurotics, only the exceptional individual is willing to continue on the diet or a slight modification for more than a few months, arriving at the conclusion that life on such a diet is hardly worth while; it is rarely possible to pursue an occupation on the rice diet or a slight modification.*

Many of these disadvantages do not apply with equal force to 200 mg. sodium diets with adequate protein and fat (page 857). It was seen above that the available evidence indicates strongly that when the blood pressure falls on the rice diet, this is due at least predominantly and perhaps entirely to the low-sodium content. Addition of adequate amounts of protein to the diet does not elevate the blood pressure. *In the experience of the writer the therapeutic effects of the 200 mg. sodium diet on the height of the blood pressure and the clinical manifestations of essential hypertension are substantially the same as those of the rice diet.* And while a 200 mg. sodium diet is far from appetizing it is much better in this respect than the rice diet, offers much more variety of food, and eliminates the dangers of protein or lipid deficiencies. Many patients are able to maintain their weight and strength on a 200 mg. sodium diet and can even follow an occupation.

For these reasons, the writer uses a 200 mg. sodium diet and not a rice diet where sodium restriction is indicated in essential hypertension. Such restriction should be given a trial in severe essential hypertension. By this is meant essential hypertension in which the diastolic pressure often exceeds 125 mm., especially if there are headaches, other cerebral symptoms or cardiac manifestations. Salt restriction should be tried if the retinal findings indicate that the hypertension is entering the malignant phase. As mentioned above, *if there is impairment of renal function rigid salt restriction is to be instituted only with great circumspection and under close observation, and not at all in the presence of azotemia.*

Is sodium restriction indicated in asymptomatic hypertension in which the diastolic pressure is not very high? For instance, should a low-salt diet be prescribed for a man who feels entirely well but has been discovered in an insurance examination to have a blood pressure of 180/110 mm.? In

. . . does not believe that the curtailment of the joy

. . . t

. . . many years away . . . The only salt restriction postpones the onset of the symptomatic stage. The only dietary limitation in such cases that seems of established value is caloric restriction to reduce obesity. Needless to say, even the least indication of cardiac insufficiency calls for salt restriction.

Innumerable hypertensive patients are being kept on "moderately" low-salt diets. Such diets usually contain 2 or 3 grams of sodium chloride daily. That they are of value in the treatment of essential hypertension, other than through suggestion and apart from patients with heart failure, has not been shown.

Alcohol.—It has been seen (page 744) that there is no evidence that alcohol as such plays any part in the causation of essential hypertension Nevertheless, because of the other effects of alcoholism, the use of large . . . 'icted strongly in patients . . . lid reason why a patient . . . not continue if he so de- . . . scontinued while weight is being reduced.

Coffee and Tea.—There is apparently no harm for most hypertensive patients in moderate quantities of these beverages Where there is marked nervousness and irritability, they should be avoided.

Tobacco.—There is also no evidence that tobacco ever produces or

. . . ulation in the lower extremities; . . . in most individuals bespeaks the . . . obacco The use of tobacco of low nicotine content, of tobacco from which much of the nicotine has been removed, or of effective filters may be of help in managing the inveterate smoker

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Chapter

29

ESSENTIAL HYPERTENSION: VI. PHARMACOLOGIC TREATMENT AND MANAGEMENT OF INDIVIDUAL SYMPTOMS

PHARMACOLOGIC TREATMENT

Ever since the hypertensive diseases were first differentiated, physicians have hoped to lower the blood pressure by antipressor drugs. *A priori*, objections have been advanced against the advisability of such pharmacologic treatment, on the theory that the rise in arterial pressure represents a compensatory and beneficent mechanism, elimination of which would harm the patient. It is true that in the presence of severe arteriosclerosis in the heart, brain or kidneys, abrupt fall in blood pressure may lead to inadequate [illegible] the absence of such [illegible] to believe that the [illegible], and this conception is completely substantiated by the improvement in headache, retinal lesions, cardiac enlargement and various other manifestations when high blood pressure is actually lowered, whatever the means [illegible] agents of the [illegible] blood [illegible]

[illegible] recent months I have seen a number of previously incapacitated patients in whom ability to pursue an occupation seemed to me to be due to treatment with the newer drugs.

[illegible] ne obser- [illegible] cerebral [illegible] blood flow is [illegible]

Nitrites.—Nitrites and nitrates which are reduced to nitrites in the body were formerly widely used in the treatment of essential and other forms of hypertension. *In fact, Lauder Brunton originally used amyl nitrite for angina pectoris on the theory, now known to be unfounded,* that it would relieve the pain by lowering the arterial pressure against which the heart works. Spaced doses of amyl nitrite, nitroglycerin, sodium nitrite, and the longer acting erythrol tetranitrate and mannitol hexanitrate have all been tried in the treatment of hypertensive diseases. In the effort to obtain a more prolonged and even nitrite action, Stieglitz[2] introduced bismuth
which nitrate ions are
. bacteria. However, in
muth subnitrate has no
demonstrable effect on the blood pressure in essential hypertension, and my findings were the same.

Nitrites lower the blood pressure in hypertensives as well as in normotensives Wallace and Ringer[4] and Weiss and Ellis[5] found that the effect of nitrites on blood pressure is proportionately about the same in hypertensives as in health, the fall being greater the higher the blood pressure. However, in
tensive encep
of blood pressure even with large doses of nitroglycerin or sodium nitrite.

Nitrites are valueless in the treatment of essential hypertension unless there is angina pectoris and perhaps in rare episodes of cerebral angiospasm The administration of doses large enough to produce significant and protracted lowering of blood pressure, if this can be accomplished at all, usually is prevented by such side effects as headache, vertigo, nausea, vomiting and faintness in the erect posture; collapse may occur Lueth and Hanks[6] found that severe reactions from nitrites are especially common in hypertensive patients, but this has not been my experience with the usual doses of nitroglycerin for angina pectoris. Nitrites appear to have no place in attempts to lower blood pressure more than momentarily.

Thiocyanates.—Thiocyanates were introduced into the treatment of arteriosclerosis and hypertension by Pauli [7] Subsequently, Nichols,[8] Westphal[9] and Gager[10] reported that thiocyanates lower blood pressure and produce symptomatic improvement in essential hypertension Davis and Barker[11] found that thiocyanate lowers the blood pressure of Goldblatt dogs. The mechanism of the hypotensive action of thiocyanate is not known The ion has sedative action, relaxes smooth muscle, may be a cardiac depressant, and affects cholesterol metabolism, as often documented by lowering of the plasma cholesterol content But that these actions are concerned in lowering blood pressure has not been demonstrated. Kessler and Hines[12] believe that the hypotensive action may be a manifestation of protoplasmic poisoning, cyanide has recently been found in the blood during administration of thiocyanate (Goldstein and Rieders) [13] Pines and Perera[14] found that thiocyanate produces sodium diuresis in hypertensives, and consider the hypothetical possibility that sodium depletion may be a factor in the hypotensive action.

Thiocyanate was formerly usually administered in solution, Elixir of Sodium Thiocyanate (N F.) is a 4 per cent solution. However, it is most

conveniently prescribed in the form of tablets, containing 65 and 200 mg. of potassium thiocyanate. The dosage is of the utmost importance because the margin of safety between the therapeutic and toxic doses is small. In

thiocyanate level be kept betw
even mild toxic symptoms do
exceeds 15 mg. per cent, and
when the serum level exceeds 40 or 50 mg. per cent (this is not in accord with other observations cited below). Corcoran[16] *et al* advise that the

toms is not sat
cautiously and
about 750 mg d
and later biweekly, and the drug withheld when the level exceeds 10 mg per cent

In some patients with essential hypertension, thiocyanate lowers the blood pressure for considerable periods and there may be symptomatic improvement Especially headache is not rarely alleviated by thiocyanate; irritability, vertigo and other nervous symptoms may also be helped Various investigators claim that symptomatic relief may also be produced by thiocyanate in the absence of change in blood pressure the same claim that is made for most methods of treatment—but it is hard to be sure that such amelioration is not due to suggestion Goldring and Chasis[17] observed definite lowering of blood pressure in 31 per cent of their patients In a survey of 1,635 cases of essential hypertension treated with thiocyanate, Lindberg[18] *et al* found that 52 per cent had a good response (fall in systolic pressure of 20 to 35 mm and 15 to 20 mm in diastolic pressure) Alstad[19] obtained a drop in basal blood pressure (page 270) of more than 15/10 mm in 62 per cent of patients treated with thiocyanate for from one to twenty months Page and Corcoran[20] observed symptomatic relief from thiocyanate in 66 of 100 hypertensive patients, though only one-quarter showed sustained lowering of arterial pressure (mean 26/19 mm)

Unfortunately, toxic manifestations often result from therapy no matter how carefully it is carried out. Even frequent control of the blood level does not completely eliminate toxic side effects If doses sufficient to lower the blood pressure are given ... tients
... con-
... drug
... rashes may occur, purpura appears rarely and severe exfoliating dermatitis has been observed. Mental confusion may occur The toxic symptoms that may result from thiocyanate therapy were studied in detail by Goldring and Chasis[17] They encountered toxic manifestations in 13

of 50 such patients. The symptoms they observed were nausea, vomiting and various cerebral disturbances such as disorientation, aphasia and hallucinations of sight and hearing. In 11 of the patients, these toxic symptoms cleared up within a few days after discontinuance of the drug. But in the remaining 2 the cerebral manifestations went on to delirium, convulsive twitchings, coma and death. One of the fatal cases had 9.77 grams of thiocyanate in fifteen days and the other 14.49 grams in eighteen days. The studies of Goldring and Chasis show that in some patients there is little or no margin of safety between the toxic and the therapeutically effective dose of thiocyanate. Garvin[21] reported a fatal psychosis due to thiocyanate therapy for hypertension which set in when the serum thiocyanate level was 13.6 mg. per cent and never went higher than 18.7 mg. per cent. In a case observed by Kessler and Hines,[12] severe nervous symptoms set in when the serum thiocyanate level was only 8.8 mg. per cent. An occasional result of protracted thiocyanate treatment is goiter, analogous to the thyroid enlargement resulting from thiourea compounds and that produced in rabbits by feeding cabbage. Hypothyroidism has resulted in some cases. Confusion and other toxic cerebral manifestations are especially apt to occur when thiocyanate is administered to elderly patients who presumably have cerebral arteriosclerosis. Impairment of renal function also predisposes to toxic effects, and thiocyanate should not be given to patients with poorly functioning kidneys.

The author administered thiocyanate to many patients with essential hypertension, especially in the first years after blood determinations came into use. In a considerable proportion there was lowering of blood pressure and, as is true with any method of treatment including placeboes, some of those whose blood pressure was not lessened had symptomatic improvement. Not uncommonly headache disappeared under thiocyanate treatment. In the malignant phase the drug almost always seemed valueless. In most patients toxic manifestations appeared sooner or later. In my experience it was rare for a patient to continue thiocyanate treatment for more than a year, and the duration of help by the drug was usually less than this. In view of the necessity for periodic blood tests, and the ever-present danger of serious toxicity, the treatment of essential hypertension with thiocyanate has not seemed worthwhile to me, and I have not used it in many years.

Sodium Nitroprusside.—Page[22] and his associates have used sodium nitroprusside in the treatment of essential hypertension. It is gradually converted to thiocyanate, but Page states that its hypotensive action is more impressive. Apparently, however, nitroprusside has essentially the same drawbacks in the treatment of essential hypertension as thiocyanate in the treatment of essential hypertension. I have no experience with the drug.

Veratrum Preparations.—For over a century veratrum viride has been known to have hypotensive action. Long used for this purpose, especially in eclampsia gravidarum, the drug was then abandoned because of the uncertainty of action of the available preparations and the frequency of vomiting and other undesirable side effects. In 1941, Goodman and Gilman's[23] authoritative text stated that veratrum viride was an obsolete

drug. Since then, however, better standardized preparations of veratrum viride and veratrum album and their constituent alkaloids have become available, and in recent years the drug has been extensively used in essential hypertension.

Veratrum viride contains at least half a dozen alkaloids having hypotensive action. In the semipurified preparations of veratrum viride on the [illegible] alkaloids are [illegible] mixture of [illegible] n veratrum album and doubtless affords more predictable results, unfortunately, it is expensive. According to Hoobler *et al.*,[26] protoveratrine by mouth causes less vomiting than the usual extracts. Several semipurified and biologically standardized extracts of veratrum viride are commercially available (Veriloid, Vertavis, Vergitryl).

Veratrum alkaloids decrease arterial pressure through lessening peripheral resistance and not, despite the usual slowing of the heart rate, through [illegible] It has [illegible]

experiments, Mills and Moyer[27] have demonstrated that veratrum alkaloids [illegible]

action. The pharmacology of veratrum alkaloids is authoritatively discussed by Krayer and Acheson.[28]

A great handicap in the use of veratrum in essential hypertension is the [illegible]

[illegible] tensive effect is obtained or nausea appears. If the blood pressure drops alarmingly with symptoms of threatening circulatory collapse, this can be [illegible]

While some patients tolerate larger amounts, Wilkins[30] found that they are rarely more effective in lowering blood pressure; my experience has been the same. Treatment with oral protoveratrine may be started with two 0.2 mg. tablets three times daily after meals. The dose may then be guardedly increased, guided by the hypotensive and side effects to as much as 2 or 2.5 mg. daily. When blood pressure is lowered by veratrum compounds, orthostatic hypotension is usually not pronounced. A feeling of warmth is common but does not call for discontinuance of the drug.

Recent interest in the therapeutic application of veratrum in essential hypertension was inaugurated by Hite's[31] observations on 30 patients treated with a biologically standardized extract (Vertavis). Sixty per cent of his patients had a reduction in blood pressure of more than 25/20 mm. Freis,[32] Wilkins and others have reported worth-while results with biologically standardized extracts of veratrum viride in essential hypertension; the blood pressure was reduced in considerable proportions of the cases over periods of many months with relief of headache and other symptomatic improvement. Wilkins finds that the oral administration of veratrum extracts produces significant hypotensive effects for days or weeks in at least 50 per cent of patients, but that as treatment is prolonged the results are less satisfactory With oral administration of protoveratrine, Meilman and Krayer[119] produced significant lowering of blood pressure in 4 of 15 hypertensives treated for three to seven months Nor do the results of Currens[120] *et al.* with oral protoveratrine in severe hypertensives seem impressive.

Other observers have had much less fortunate results with extracts of veratrum viride In 22 patients treated with Vertavis for two to five months, and controlled by placebo tablets, McNair[33] and his associates did not observe a statistically significant hypotensive effect. Similar unsatisfactory results were obtained by Coe[34] *et al.* with Vertabis in 25 ambulatory hypertensive patients. Gropper[35] *et al* treated 35 hypertensive patients with Veriloid, first in the hospital and then as out-patients In the hospital the drug lowered the average diastolic pressure 15 mm or more in 12 of the cases, while in the out-patients' department only 6 were similarly lowered Mills and Moyer found that of 30 hypertensive patients given an average daily dose of 18 mg. of alkavervir (Veriloid) per day, 50 per cent had a hypotensive response more than 20/10 mm , but in only 1 was the blood pressure reduced to normal levels

The therapeutic results of the writer with veratrum preparations in essential hypertension have been very modest (apart from the parenteral use in hypertensive encephalopathy). In the attempt to use doses large enough to produce a significant decrease in blood pressure, nausea and vomiting were evoked in a high proportion of the patients One can often reduce the blood pressure about 30 15 mm. and exceptionally more. But it usually is not long before nausea and vomiting appear or the blood pressure rises again as the patient gets about after the medication is inaugurated at rest. I have seen few cases in which veratrum treatment seemed worthwhile, and it has been rare in my experience that patients with severe hypertension continued to take veratrum preparations for more than a few months. In patients in the malignant phase of essential hypertension,

veratrum has been completely disappointing for other than parenteral use in encephalopathy.

Injection of Veratrum Preparations.—A preparation of alkavervir (Veriloid Intravenous Solution) is available for intravenous injection. The hypotensive effect of this solution is extremely powerful and it must be given with the utmost care. By intravenous administration it is possible to lower the blood pressure of almost all hypertensive patients. Wilkins gives the average intravenous dose of Veriloid as 0.75 to 1.0 microgram per kilogram body weight per minute. Veriloid Intravenous Solution is sup- [illegible] Veriloid Standard refer- [illegible] The makers advise that [illegible] be drawn into a 10 cc. [illegible] syringe and diluted to 10 cc with 5 per cent glucose or isotonic sodium chloride solution. The diluted solution is injected as follows: 0.5 cc per minute for eight minutes, pause for 2 minutes, 0.5 cc per minute for six [illegible]

[illegible] irregular, or nausea or vomiting develop. After the blood pressure stabilizes, the injection can be continued in the same slow fashion until a level of about 150/100 mm is reached. If the original 10 cc does not suffice, another similar injection can be started. An attempt may then be [illegible] continuous [illegible]

[illegible] usual patient the effective dosage does not exceed 100 cc per hour. The infusion may be continued for hours or days. Needless to say, the patients must be watched continuously and the blood pressure determined at frequent intervals. Arterenol solution should be available and given by intravenous drip in case of excessive fall in blood pressure; the marked bradycardia which usually accompanies overdosage is combated by atropine sulfate.

Intravenous administration of alkavervir may be spectacularly helpful in hypertensive encephalopathy in essential hypertension, the toxemia of pregnancy or nephritic hypertension. Such cerebral manifestations as intractable headache, nausea, vomiting, convulsions and amaurosis may clear up as the arterial pressure is lowered. Veratrum should not be given in hypertensive paroxysms in pheochromocytoma.

Methonium Salts.—These recently synthesized ganglionic blocking agents are perhaps the most powerful hypotensive agents available to the clinician. Their present extensive use in the treatment of hypertensive disease is largely due to extensive studies of Smirk.[45] Burn and Dale[36] long ago showed that tetraethylammonium chloride blocks the transmission of nervous impulses through autonomic ganglia, both sympathetic and parasympathetic. This is perhaps due to competition for acetylcholine. Paton and Zaimis[37] studied the pharmacologic properties of the chemically related methonium series, which had shortly before been prepared by Barlow and Ing,[38] and found that the pentamethonium (C5) and hexamethonium (C6) members are even more potent than tetraethylammonium in blocking autonomic ganglia. The hexamethonium salts have ganglionic blocking activity of the order of five times that of tetraethylammonium chloride; their action lasts about 5 times as long (Finnerty and Freis[39]). As a result of the blockade of the sympathetic ganglia, blood flow through the upper and especially the lower extremities increases (Arnold[40] *et al.*, Burt and Graham[41]). Finnerty and Freis found that hexamethonium produces a greater and more prolonged rise in digital skin temperature than do either Priscoline or tetraethylammonium Observations by Schnaper[42] *et al* indicate that 50 to 100 mg. of C6 intravenously increases blood flow through the foot about as much as does lumbar block. The vasodilatation produced by methonium salts lowers the blood pressure, especially in the erect posture, so that orthostatic hypotension results. The above investigators and Restall and Smirk[43] found that C5 and C6 lower the blood pressure of hypertensive patients. Restall and Smirk's observations indicate that this hypotensive effect is at least partially due to relaxation of blood vessels in dependent parts with resultant pooling of blood and decrease in venous return to the heart. The blood vessels in the kidneys (page 879) and brain (Crumpton and Murphy[122]) are dilated. While Freis[123] *et al.* found the same true in the splanchnic area, Reynolds[124] and his associates observed unaltered splanchnic resistance in 15 of 17 subjects. That the hypotensive effect is due to diminished total peripheral resistance is shown by the finding in some cases of unchanged cardiac output (Freis *et al.*) The heart rate is accelerated.

Unfortunately, methonium compounds impede not only transmission across the sympathetic ganglionic synapses of the impulses that produce vasoconstriction, they also call forth other consequences of sympathetic and parasympathetic blockade. The latter constitute a grave handicap in the use of hexamethonium in hypertension. These atropine-like side effects are very variegated and include· Diminution in intestinal peristalis with resultant constipation, tympanites and very rarely even paralytic ileus, dryness of the mouth, diminution in gastric secretion and motility sufficient to suggest trial of methonium compounds in the treatment of peptic ulcer (Kay and Smith[44]); urinary retention, diminished potency; difficulty in rea [illegible]
times evinced [illegible]
days. Fatal p[illegible]

Hexamethonium salts are poorly and irregularly absorbed from the alimentary tract. A large part is lost in the stools. Hexamethonium was

intramuscular or intravenous injection.

trically operated syringe for the continuous subcutaneous injection of methonium halides. He has also tried slowly absorbed methonium preparations. Recently, however, oral administration of hexamethonium chloride has become the most widely used therapeutic method (use of the bromide by mouth may induce bromism). The oral dose is usually more than ten times that by injection. No matter by what route hexamethonium is administered, the individual variation is so great that the initial dose should be very small. The drug should be started only when the patient is under close observation and carefully instructed regarding side-effects and manifestations of overdosage. Especially if hexamethonium is given by injection, treatment is best inaugurated in the hospital Unpleasant hypotensive reactions are most apt to follow the

because such a procedure fixes attention closely, and often undesirably, on the height of the blood pressure

If it is decided to start hexamethonium parenterally, the preferable procedure, this is almost always best done in the hospital. Freis[47] and his coworkers determine the initial dose by intravenous injection with the

ute until an additional 10 mg has been given, and then 5 mg per minute to a maximum of 50 mg of the ion. The injection is discontinued as soon as the blood pressure falls, if the drop in profound the pillow is removed

5 mg. of phenylephrine

ously. The effective

every eight to twelve

rements to a maximum of 50 mg. or rarely even more, if such amounts are needed to obtain significant hypotensive response

The writer has not used intravenous injection of hexamethonium but has started treatment with very small doses subcutaneously and increased gradually. The drug is injected with the patient seated in a chair or propped up high in bed so as to take advantage of some of the orthostatic

injection and until the optimum dosage is determined Especial care should be taken with patients whose renal function is impaired or who have undergone surgical sympathectomy, for they may be extremely sensitive to the hypotensive effect of hexamethonium The initial injection may be 2.5 or 5 mg of hexamethonium ion 2 or 3 times daily, this may be increased by 5 mg. an injection the second day and then by 10 mg an injection until a substantial hypotensive response is obtained. Tolerance usually develops

rapidly so that a patient who at first has a hypotensive response to 10 to 50 mg. doses may later require 100 mg. of the ion or even more. Patients on hexamethonium therapy must be warned to assume the recumbent position if giddiness develops. After several weeks the dosage may become relatively stabilized at an amount which lowers the blood pressure substantially and need not be raised for months. However, in the severe hypertensives in whom alone I have followed the effects of hexamethonium, the stabilization—relative at best—has been at blood pressure levels well above the normal, though below that previously existing. In order to obtain the help of the orthostatic element in the hypotensive effect, the patient should, as advised by Smirk, be seated or standing as much as possible and sleep with the head of the bed elevated. With the head of the bed elevated, it appears that a lower blood pressure is maintained for a larger part of the time with a given dose.

Recently, hexamethonium chloride has been more often given by mouth. Though the results are decidedly less dependable than by injection, the latter is often not feasible for ambulant patients. The initial dose should be very small and then gradually increased A start may be made with 125 mg. before breakfast and dinner. The dosage may then be gradually increased to 2000 or less often 3000 mg. daily The latter amount should rarely be exceeded because of side-effects, though as much as 6000 mg. daily have been given Rather than exceed 3000 mg. daily with the almost inevitable side-effects, it is advisable to give hexamethonium by injection. The drug is usually given at six hour intervals; it should not be given more often than every four hours because of danger of summation of two doses Patients must be warned immediately to assume the horizontal position if vertigo or faintness develop and also informed of the possible side-effects of the drug (page 880) If either hypotensive manifestations or side-effects appear, no further doses should be taken without prior consultation with the physician Patients should be cautioned against standing still for long periods because of the danger of syncope from orthostatic hypotension. Through inhibiting intestinal peristalsis, hexamethonium tends to produce constipation and tympanites This is dangerous because the usual small percentage of the drug absorbed from the bowel may then be increased with resultant overdosage. The patient should take a mild cathartic (milk of magnesia and cascara) every night, should this fail, a saline cathartic should be given Impotence is common but disappears during omission of a few doses. Should there be urinary retention or ileus, Urecholine or neostigmine may be given. Marked lowering of the blood pressure may be accompanied by continuous lassitude and then call for diminution in dosage

The hypotensive action of the drug appears to be potentiated by sodium restriction; the latter should be maintained while the patient is getting the drug. Some individuals who have undergone sympathectomy are also highly sensitive to hexamethonium. Elderly arteriosclerotic patients are subject to sudden hypotensive episodes and side-effects on relatively low dosage and probably should not be treated with hexamethonium The use of hexamethonium in the presence of coronary or cerebral arteriosclerosis or severe impairment of renal function carries with it the danger of inade-

quate perfusion of the organ in question. I have seen several instances of coronary insufficiency due to hexamethonium *Death from circulatory collapse due to overdosage with hexamethonium has occurred* (Campbell[?] *et al*). . . . . studied by

e that when

hexamethon-

by a propor-

tionately greater depression in urinary volume and sodium excretion, while maximum tubular excretion (PAH Tm) is unaffected. However, compensatory mechanisms come into play, for glomerular filtration rises again while the blood pressure is still depressed. The above mentioned investigators found that the depression of glomerular filtration lasts longer when renal function is already impaired, a finding which points to the need for caution in using the drug in such patients. When blood pressure is reduced by protracted oral administration of hexamethonium, Ford[12] *et al.* found that renal plasma flow, glomerular filtration rate and *tubular excretory* capacity are unaltered; these observations show *that the renal* vessels participate in the vasodilatation

Several investigators have reported worth-while results from hexamethonium in essential hypertension The first detailed clinical studies were carried out by Smirk[45] and his associates In 53 patients with severe essential hypertension (including 11 in the malignant phase), they were able by subcutaneous injection of hexamethonium bromide to obtain worth-while hypotensive action In many, the blood pressure was kept at

rhythm disappeared in 4 of 5 patients Most significant is their observation that in all of 11 patients who were treated for two months or more, papilledema either disappeared or substantially lessened Retinal hemorrhages and soft exudates likewise improved The results of Freis *et al.* were also favorable, though not as good as those of Smirk In 33 patients with

with hexamethonium and hydralazine Of 16 patients with less severe essential hypertension, 6 had sustained reduction in blood pressure from hexamethonium alone and 4 others from the combination of hexamethonium and hydralazine, most of the unsuccessful cases were treated with too small doses They used hexamethonium subcutaneously in doses of 10 to 75 mg of the ion twice daily and preferably in combination with oral hydralazine (see below) With both oral and subcutaneous administration of hexamethonium, Campbell *et al* obtained symptomatic and manometric improvement in 23 of 35 hypertensive patients whom they treated for up to two years They observed improvement in five patients whose blood pressure was elevated as a result of chronic nephritis Moyer[125] and his associates treated 120 hypertensives with oral hexamethonium for 3 to 18 months, a high proportion were severely ill All but 17 responded with significant *decrease in blood* pressure, and of those treated for more than a

year 64 per cent were regarded as well controlled. They found patients with cardiac failure and moderate to severe renal disease especially resistant to therapy. Sieber[126] *et al.* administered hexamethonium to 50 patients with severe, stable or progressive hypertension (46 by mouth) for an average of nine months. The blood pressure in the recumbent position was reduced to 160/110 mm. or less in 40 per cent of the patients while they were in the hospital, in 16 per cent during the first four months of outpatient care, and in only 6 per cent in the subsequent 5 to 19 months. In 15 patients treated for an average of 7 months with oral hexamethonium, Hilker[127] *et al.* obtained in the recumbent position a significant systolic fall in 60 per cent, but the diastolic pressure decreased similarly in only 13 per cent of their patients; the corresponding percentages when erect were 93 and 47, indicating the high degree of orthostatic hypotension. The hypotensive effect of hexamethonium is usually accompanied by symptomatic improvement, such as relief of headache, clearing of retinopathy and decrease in the size of the heart.

Unfortunately, hexamethonium has many undesirable and even dangerous actions. The consequences of parasympathetic blockade were mentioned above (page 876) Overaction may produce severe orthostatic hypotension; vertigo and syncope may result from cerebral ischemia. In patients with coronary arteriosclerosis, dangerous coronary insufficiency may develop; one such case was fatal With impairment of renal function, the hypotensive effect of hexamethonium may augment azotemia and apparently precipitate clinical uremia In patients with cerebral arteriosclerosis, also, hexamethonium may produce manifestations of inadequate cerebral blood flow and rarely even infarction. Peculiar pulmonary infiltrations were observed by Morrison[128] in a few of the patients he treated for a long time with hexamethonium. Similar observations were made by Schroeder[129] following combined use of hexamethonium and hydralazine; he describes the lesions, which produced tachypnea and were fatal in 4 of his patients, as interstitial pneumonia. Schroeder has measured the hexamethonium level in the blood; he states that amounts in excess of 1.0 mg per cent are abnormal and that severe symptoms can occur with levels of 2.5 mg. per cent It may well be that in the future hexamethonium treatment will be guided by study of blood levels.

Hexamethonium is a potent hypotensive agent But it is also a dangerous drug and few patients escape without side effects. The use of hexamethonium represents a calculated risk, and one which should not be taken without careful evaluation of the pros and cons in each individual case. However, in a considerable number of patients under my observation with severe forms of essential hypertension the risk was proved worth taking by excellent therapeutic results; in a few of these in the malignant phase of the disease as proved by papilledema, the symptomatic improvement, lowering of blood pressure and clearing of the retina has by now lasted almost a year.

The use of hexamethonium in congestive heart failure has been suggested by Kelley[51] *et al.* They find that in congestive failure of various origins, the drug lowers elevated venous pressure and usually circulation time and heart rate with improvement in dyspnea. These beneficial effects are attributed

to reduction in peripheral resistance and peripheral pooling of blood with consequent decrease in cardiac work and overloading of the right heart. In the one cardiac patient in whom Kelley and his associates measured cardiac output, it was increased in the face of lessened total peripheral resistance. The effects of hexamethonium on the pathological physiology ... is therapeutically

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... (laboratory number ...) and is mar-
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... nerular
... output,
filtration (Moyer[34]). Hydralazine increases the ... output, which apparently results from central sympathetic stimulation and disappears with continued use of the drug before the hypotensive effect does ... have found in man that a single

tionately as much as was cardiac output. Since the skin temperature ... not raised, it appeared that the vasodilatation was predominantly splanchnic. That the cerebral vesse... was ... et al shown by measurements of ... azine Wilkinson et al. showed that ...

tensive effect of hydralazine has not been completely elucidated. Grimson[33] et al. found that the drug blocks pressor reflexes. There is some evidence that the action may be a central one on the vasomotor centers or ... Wilkinson

... of such humoral and the ... To what extent each of these mechanisms participates in the depressor effect of hydralazine has not been elicited.

treatment should be started with small doses, e. g., 10 or 25 mg twice daily after breakfast and dinner. The second day 25 mg may be given 4 times daily, after meals and before retiring. After a week, the dosage is slowly increased by augmenting the size of one or more of the four doses.

Most often the maintenance dose is about 400 mg. daily, but 800 mg. and even more has been given in some cases.

Use of hydralazine is often handicapped or prevented by distressing side-effects. Since in the therapeutically employed doses hydralazine usually has not as potent a hypotensive action as hexamethonium, orthostatic hypotension or manifestations of excessive fall in blood pressure are much less common than with the latter drug. The most common side-effect is headache; it is usually occipital and may be very severe and pounding, forcing discontinuance of the drug. Since the headache may be accompanied by nasal and conjunctival congestion, it has been attributed to an anti-histaminase action of hydralazine and treated with antihistamines; the latter, however, have not always helped in my experience. The headache may conceivably be a result of dilatation of cranial blood vessels as in migraine. The headache often disappears if hydralazine is continued for a week or two in smaller doses, but sometimes it forces discontinuance of the drug. Vertigo, nausea, vomiting, palpitation, abdominal cramps, frequent urge to defecation, flushing, facial and other edema, numbness and tingling of the extremities, joint pains, and drug rash may occur. High fever (105°) forced discontinuance of the drug in one patient. Low grade fever with bodily pains is not rare, it usually disappears in a few days. With pronounced drop in blood pressure in uremic or other severely ill patients, such cerebral manifestations as depression and anxiety may occur; on very rare occasions, even coma has been observed. A remarkable toxic effect of hydralazine has been reported by Dustan[130] and her associates. In 13 of 139 patients treated with large doses of hydralazine for long periods, they observed a syndrome resembling rheumatoid arthritis or, in its more severe form, disseminated lupus erythematosus; one of the patients had a positive L.E test in the plasma and another L.E cells and rosets in the bone marrow. The syndrome usually disappeared spontaneously; in two of the cases ACTH was effective I saw two similar cases with febrile arthritic manifestations Kaufman[60] has reported an instance of pancytopenia due to hydralazine.

While hydralazine has been extensively used in the treatment of essential hypertension in the past year, the time elapsed has not been sufficient to assess its actual value. Schroeder gave hydralazine to 50 hypertensive patients for from 1 to 40 weeks The diastolic pressure was lowered 20 mm. or more in 35 instances, but in only a few of the mildest cases was a sustained reduction to normal levels attained The symptomatic results apparently were not very impressive, although he observed improvement of depressed renal function and retinopathy in 2 patients after two to three months treatment Page[61] gave hydralazine to 70 hypertensive patients in doses of from 100 to 1400 mg daily The diastolic pressure was reduced 20 mm. or more in 33 of the patients; in several the malignant syndrome was reversed He found that the blood pressure fell first in the erect posture and only later when reclining. In some of the patients good responses were not obtained until after ten days of treatment Later, Taylor[62] *et al.* reported that of 97 patients treated with hydralazine, a quarter had a drop in diastolic pressure to normal and another third to less than 110 mm ; their results were most often favorable in cases which they re-

garded as neurogenic, for which reason they believe the drug may act on a cerebral pressor mechanism. Mills and Moyer[84] obtained a reduction of blood pressure more than 40/20 mm. in the erect posture in only 2 of 13 ambulant hypertensive patients given an average daily dose of 400 mg. of

alkavervir.

hydralazine

In a careful

study, Moyer[84] found that at the end of a year only 9 of 52 hypertensive patients started on hydralazine still took the drug, and of these only 5

are. In my

the start or

majority of

patients in whom it is started. Moyer found ST-segment depressions and T wave changes in many patients in whom a hypotensive response was obtained; I observed fatal coronary insufficiency in 1 case.

Combined Use of Hexamethonium and Hydralazine.—Several considerations point to the possibility that the combined use of hexamethonium and hydralazine may be more efficient than either drug alone. Moyer points

different substrata If either drug is administered at long intervals, the

hydralazine in alternating doses Schroeder's technique is as follows: Treatment is inaugurated in the hospital (Schroeder refers to treatment with hexamethonium and hydralazine as treatment with "Hyphex"). Schroeder teaches the patient or a relative to measure the blood pressure so that the doses of the drugs can be varied in accord with specific directions Hexamethonium chloride is given orally in doses of 125 mg every

arting with 25

100 mg. every

hours has been reached or "the blood pressure had become normotensive" (so favorable a result did

in the severe cases that I have seen)

individual cases With this plan

cellent results. Of 20 patients with

hospital, 14 attained normotensive levels of 140/90

the malignant state was reversed in 13. Schroeder[129] found that in malignant hypertension cessation of Hyphex almost always proved fatal within a few days or weeks as a result of heart failure, uremia or a stroke. For this reason, Schroeder emphasizes that if Hyphex treatment is begun in malignant hypertension, it must be continued. *Because of this danger, I have not attempted full-scale treatment with hexamethonium plus hydralazine in the malignant phase of essential hypertension. However, in patients treated with hexamethonium alone or hexamethonium plus smaller doses of*
cessation of treat
the reader is referred to his recent monograph and articles.[131]

The use of hexamethonium is discussed further below (*page 887*).

Hydrogenated Ergot Alkaloids.—These have recently been employed in the treatment of both hypertensive and peripheral vascular diseases. This application followed Stoll's[66] finding that ergotoxine consists of three alkaloids—ergocornine, ergocristine and ergokryptine—and that, while the dihydro-derivatives of these alkaloids lack the ability of the naturally occuring alkaloids to stimulate smooth muscle, they are powerful sympathetic blocking agents. Rothlin[67] found that these hydrogenated ergot-alkaloids lower both normal and elevated blood pressure and suggested their use in hypertension. According to Nickerson,[68] the hypotensive action is due predominantly to central depression of the postural cardiovascular reflexes and central stimulation of the vagal nuclei. Bluntschli and Goetz[69] attribute the lowering in blood pressure only to central inhibition of sympathetic impulses, for they observed it after atropinization. The hypotensive effect has an orthostatic component and is accompanied by slowing of the heart rate. Renal blood flow and glomerular filtration are

e under the name
of ing 0 1 mg each
of ergocristine and
dihydroergokryptine. The systolic and diastolic pressures are lowered by intramuscular or intravenous injection of the alkaloids; they have also produced hypotensive effects by mouth, but the amounts required are too expensive for practical use and Bello[71] *et al* obtained no consistent effects on the blood pressure even with large oral doses of dihydroergocornine. The dosage recommended is 1 cc. of Hydergine (0.1 cc. of each of the three alkaloids, which are said to potentiate one another) intramuscularly This is first given daily and then the dosage is gradually increased Attainment of a hypotensive effect may be prevented by nausea and vomiting, the alkaloids stimulate the emetic center. Stuffiness of the nose and weakness are occasional side-effects.

Favorable results with hydrogenated ergot alkaloids in essential hypertension were reported by Goetz,[72] Josephs,[73] Gibbs,[74] Nuzum[75] and others. Nuzum obtained an average lowering of blood pressure of 42/16 mm. and subjective improvement in patients with essential hypertension who were given Hydergine for sixty days; the improvement is said to have lasted two or three months after cessation of the drug. Contrariwise, Dupuy[76] and Sutton[77] and their respective associates find Hydergine of little value in the

long-range treatment of essential hypertension. My experience has also been that, while it is possible to lower modestly the blood pressure of some patients with hydrogenated ergot alkaloids, the effect is not sufficiently pronounced to be worthwhile in actual treatment. Tandowsky[132] found that intravenous injection of 1 cc. of Hydergine in saline often relieves severe hypertensive headaches and other cerebral manifestations.

... nd in

symptoms and believes that it acts on the nervous system. Rauwolfia has recently been introduced into the United States by Wilkins and Judson for the treatment of essential hypertension. They find that it is well tolerated, sometimes has moderate hypotensive action, and often produces excellent symptomatic improvement. Among the side-effects described by Wilkins and Judson[79] are sedation, ... gain in weight. Nightmares may occu... as the powdered root (Raudixin) in 50 ...

. An ... id; it ... ntly, ... Ciba) ... hole root

as restlessness, irritability, insomnia, palpitation and headaches of not extreme severity In some of these patients the sedative action of Rauwolfia seemed to be superior to that of barbiturates The bradycardiac effect may be helpful While Rauwolfia had a modest hypotensive effect in some of the cases, this was not marked In a few patients in the malignant phase of essential hypertension, Rauwolfia had no significant effect. In 30 hypertensive patients treated by Wilkins and Judson, the average

combination of hexamethonium and Rauwolfia produced an adequate reduction of blood pressure in a higher combination which they tried. I have also seen some worthwhile results from this combination.

Other Adrenergic Blocking Agents.—Tetraethylammonium chloride and bromide are the classical autonomic ganglionic blocking agents and reduce arterial pressure in normotensive as well as in hypertensive patients for up to about eight hours after intramuscular injection Postural hypo-

...pertension But they did not find it of value in the treatment of es-

sential hypertension. My experience was similar. Death has followed use of the blocking agent in essential hypertension (Lasser[51] *et al.*). The effect of tetraethylammonium chloride has been suggested as a test for the advisability of sympathectomy, but Burchall[52] *et al.* found no parallelism between the change in blood pressure produced by the drug and the outcome of subsequent sympathectomy.

Priscoline likewise, despite production of adrenergic blockade and peripheral vasodilatation, has been of little benefit in hypertensive disease (Grimson[53] *et al.*). Nickerson attributes the failure to obtain a hypotensive effect, and the occasional elevation of blood pressure, to strong cardiac stimulation by Priscoline which overbalances the peripheral dilalation.

Dibenamine hydrochloride is a potent adrenergic blocking agent Haimovici and Medinets[54] administered 5 mg./kg by intravenous infusion to both normotensive and hypertensive subjects. The effect on the blood pressure of normals was variable but there was a significant reduction in blood pressure of patients with "benign" essential hypertension; those with malignant hypertension had little change. Contrariwise, Wunsch[55] *et al.* did report temporary lowering of blood pressure and symptomatic relief from dibenamine in malignant hypertension, especially in episodes of hypertensive encephalopathy. Bridges and White[56] also observed lowering of blood pressure in less severe forms of hypertension. However, the actual therapeutic value of dibenamine in essential hypertension, with which the writer has no experience, has not been demonstrated.

An orally administered dibenamine derivative (laboratory number 688-A), which produces adrenergic blockade, has been used in 11 patients with essential hypertension by Moser[57] *et al* There was significant fall in diastolic pressure in the recumbent position in 5 and when erect in 9 patients. The writer has no experience with this blocking agent.

Regitine has been tried in the treatment of essential hypertension (*cf.* Grimson[58]), but Moyer and Caplovitz[59] found it useless for other than the temporary relief of hypertensive crises.

Value of Pharmacologic Agents in Essential Hypertension.—In summary, the writer's experiences with and impressions of the drugs just enumerated are as follows.

Thiocyanates - In doses sufficient to lower the blood pressure and produce results other than those due to suggestion, coincident rest or salt restriction. the incidence of distressing side-effects is very high and usually forces discontinuance of the drug The use of thiocyanates does not seem worthwhile to me

Veratrum Preparations The margin between the hypotensive dose and that producing undesirable or intolerable side-effects is usually small or absent. In the malignant phase, veratrum preparations have not been effective in my experience. I have known few instances of essential hypertension in which veratrum preparations have seemed to help the patient. An exception is, however, parenteral injection of purified veratrum derivatives, which may be of great value in the treatment of hypertensive encephalopathy.

Hydrogenated Ergot Alkaloids.—It is often possible to produce some lowering of blood pressure with these drugs. However, the effect is rarely pro-

nounced and unpleasant side-effects are common. The use of these alkaloids has not seemed worthwhile to me in the few cases in which I have observed their use

Tetraethylammonium chloride, *Priscoline* and, from the literature, *Dibenamine* seem to be valueless in the long-term treatment of essential hypertension.

Hydralazine —Significant and protracted lowering of blood pressure is produced by hydralazine in only a small minority of patients with severe

1. Even if it was a purely adrenergic blocking agent, which it is not, the hexamethonium ion does not have an established rationale in essential

2. Hexamethonium salts block not only sympathetic ganglia and thus

always used hexamethonium in association with sodium restriction, this has been without the needed justification of a control series of patients treated with hexamethonium but no sodium restriction In using hexamethonium, the following limitations should be borne in mind

1. The use of hexamethonium in doses sufficient to produce a significant effect is always trying to the patient and not without danger Nothing is known of the long-term effects of the drug For these reasons hexamethonium should not be given in mild cases of essential hypertension in the hope of preventing progression As a rule the drug is not called for unless there are headache or other symptoms, or retinopathy or a very high diastolic pressure bespeak the likelihood that the symptomatic stage is not far off.

2. Hexamethonium should not be used in patients with coronary insufficiency or symptoms of cerebral arteriosclerosis for fear of precipitating ischemic manifestations In the presence of unpairment of renal function severe enough to produce azotemia, the danger of precipitating uremia through decreased renal blood flow should be borne in mind. Even if the

impairment of renal function is revealed only by hyposthenuria without azotemia, great caution should be used in administering hexamethonium; in my experience the results have not been worthwhile and side-effects have necessitated discontinuance of the blocking agent.

3. In elderly arteriosclerotic patients with predominantly systolic hypertension, great and irregular fluctuations in blood pressure may be produced by hexamethonium and severe reactions are common. Such patients usually suffer more from arteriosclerosis than from hypertension, and the use of hexamethonium is inadvisable.

4. The abrupt fluctuations in blood pressure that are the rule in hexamethonium treatment are not without danger, especially in malignant hypertension. From too rapid reduction in blood pressure, Schroeder observed uremia, cerebral vascular accidents and multiple myocardial infarctions. I have made similar observations.

. . . .

be followed by what seems to be an overshooting which may be dangerous.

Much more experience over protracted periods will be required before the place of hexamethonium in the treatment of essential hypertension is established. But it is worthy of a trial in all instances of severe essential hypertension in which none of the above-mentioned contraindications exist. Especially in patients with very high diastolic pressure and headache, the drug may lower the pressure and produce great symptomatic improvement for periods which are already known to be as much as a year and further experience may reveal to be much longer. Great improvement may occur in patients in the malignant phase, including clearing of hypertensive retinopathy. It would appear that in at least most instances hexamethonium should be tried before surgical sympathectomy is advised. Hexamethonium appears to be more effective when sodium is restricted in the diet, and such restriction should be maintained. As mentioned above, the combination of hexamethonium and Rauwolfia appears often to be a valuable one. To some extent this may be due to opposite effects on the rate of the heart; it sometimes appears that the blood pressure may be lowered with fewer side-effects than with hexamethonium alone. Recently, I have usually initiated treatment with Rauwolfia and then added hexamethonium; in extremely severe cases, this sequence may be reversed by starting with hexamethonium, incomparably the more powerful hypotensive agent.

Rauwolfia Serpentina.—Experience with this drug has as yet been brief. It is not a potent hypotensive agent and hardly seems of avail in the malignant phase of essential hypertension. In less severe cases with such symptoms as palpitation, restlessness, fleeting headaches and tachycardia the sedative and bradycardic actions of the drug may be of help. The combined use with hexamethonium has just been mentioned.

Most of the newer hypotensive agents are expensive. Their use has been encouraged by extremely active advertising to physicians. Many asymptomatic hypertensives who would be better off without treatment have been put to great expense and some danger of untoward side-effects by the use

of these hypotensive agents as little more than placeboes. If a placebo must be used, and this is rare, it should be a cheaper and safer one.

Sedatives.—These drugs are prescribed for almost all hypertensive patients at one time or another. They are particularly useful in the numerous patients who are anxious, worried and irritable. In these cases one not uncommonly sees some drop in blood pressure, usually not marked, accompany the use of sedatives. Even if the blood pressure is unaffected, the nervous symptoms may be ameliorated. *Chloral hydrate and phenobarbital* are among the most generally useful sedatives If the chloride

patients, but it usually became less effective on prolonged administration. Actually when the blood pressure is lower following the use of sedatives, it

other hand, Adams and Brown[93] found that nonspecific protein therapy (injection of typhoid vaccine) had no effect in severe cases of essential hypertension

do not use the pyrogen treatment in patients with severe impairment of renal function. They employ a soluble bacterial pyrogen (Pyromen, Baxter Laboratories), starting with intravenous injection of 0.5 cc The injections are given 5 or 6 times weekly in amounts sufficient to produce a temperature of 103° or 104°; this requires increasing dosage With this procedure

and other evidences of reversal of the malignant phase If the fever is tolerated poorly, Page and Taylor make the patient more comfortable with aspirin or aminopyrine, though this renders it more difficult to judge the dosage The writer has no experience with the pyrogen treatment of essential hypertension, which seems rather strenous and demanding on the patient

It seems probable that the pyrogenic reaction plays a part in the lowering of blood pressure which sometimes follows some methods of treatment initially regarded as specific:

Kidney Extracts.—Grollman[95] *et al.* and Page[96] and his coworkers prepared extracts of kidney which reduced the blood pressure of hypertensive dogs and of patients with essential hypertension. The extracts of the first group of investigators were given both orally and parenterally, those of Page *et al.* parenterally. It seems likely that at least much of the hypotensive effect of the parenteral injections was due to a pyrogenic effect. Observations by Goldblatt[97] *et al.* indicated that it is especially when injections produce abscesses that the blood pressure of hypertensive dogs is lowered.

Tyrosinase.—Based on the hypothesis that phenolic amines may be concerned in hypertension (page 333), Schroeder[98] attempted to treat hypertensive disease with tyrosinase prepared from mushrooms. However, Prinzmetal[99] and his associates showed that similar hypotensive effects are produced by heat-inactivated preparations of tyrosinase They are probably due to local inflammatory and pyrogenic reactions.

Sex Hormones.—On page 714 it was seen that such an entity as menopausal hypertension does not exist and that the administration of estrogens does not lower the blood pressure of hypertensive patients Estrogens are indicated in hypertensive women only if they have symptoms which would call for hormones in the absence of hypertension Apart from the amelioration of such specifically climacteric manifestations as hot flushes and sweats, estrogenic medication may be followed by alleviation of restlessness, emotional instability, headache and various other "nervous" symptoms. The correlation of these symptoms with the climacteric rather than the hypertension is often revealed by improvement on estrogenic treatment without change in blood pressure. However, as might be anticipated, the relief of the emotional tension of the climacteric often results secondarily in somewhat lower blood pressure in hypertensive women.

Testosterone is often given to hypertensive men, but there is neither rationale for its administration nor evidence that it is of value for other than symptoms of androgenic deficiency which would call for the hormone in the absence of hypertension.

Vitamin A.—Govea-Pena and Villeverde[100] reported that large doses of vitamin A (100,000 to 200,000 units daily by mouth) have a hypotensive effect in essential hypertension. However, Taylor[101] and his associates found even larger doses valueless, although they did produce renal vasodilation and increased secretory capacity of the kidney for diodrast. In several cases I saw no effect of vitamin A on the blood pressure in essential hypertension.

Other Drugs.—Among the host of other drugs which have been advocated for the treatment of hypertensive patients are the following: Iodides, benzyl benzoate, extract of watermelon seeds, radium chloride, thyroid extract, liver extract and pancreatic extract References to the literature on these remedies will be found in the Fourth Edition of this book, none of them appear to help other than by suggestion

MANAGEMENT OF INDIVIDUAL SYMPTOMS

Cardiac Manifestations.—In many patients with essential hypertension, the cardiac features are so predominant that treatment consists in little

more than combatting heart failure, angina pectoris or myocardial infarction.

Heart Failure.—The treatment of heart failure in essential hypertension is fundamentally the same as in normotensives. Rest, sodium restriction, digitalis, mercurial diuretics, control of arrhythmias and weight reduction in the obese are the basic measures. The principal modifying circumstance ... the state of renal function, which is much more

tensive heart fails the possibility of myocardial ... ered and, if found, appropriate treatment instituted.

Rest is of even more importance when the hypertensive heart gives way than in other forms of cardiac insufficiency. This is perhaps because in the case of cardiac failure due to hypertension, bed-rest helps the heart not only by reducing the added quota of work from physical activity, which it also does in rheumatic and other forms of heart disease, but is also often of additional aid by lowering the blood pressure. Quite probably, in some of the cases of "Hochdruckstauung" (page 789) in which it has been thought that the blood pressure is lowered as a result of improvement of the heart, the actual sequence of events is
as it often does in the absence o

arteriosclerosis are absent. With the first appearance of exertional or paroxysmal dyspnea, cough, swelling of the liver, edema or other mani-

tensive heart failure early ambulation is often not as desirable as in other forms of cardiac insufficiency, the blood pressure is usually lower while the patient is in bed with resultant decrease in the work of the heart.

Sodium Restriction is often of sovereign help in the treatment of heart failure in hypertension. In many instances, presumably, decreasing the ... other ... sodium ... below
500 mg daily. Moreover, sodium restriction should be continued after compensation has been restored, as a prophylactic of subsequent failure. Sodium intake should be lowered only cautiously when renal function is severely impaired because inadequate conservation of sodium by the kidneys may then lead to sodium depletion and the low-salt syndrome.

It is true that in animal experiments digitalis raises the blood pressure not

vasoconstriction. In man, however, this pressor action seems to be slight or absent; in fact, the blood pressure, notably the diastolic, often falls as the heart improves under digitalis. Nor has the presence of a high degree of coronary arteriosclerosis, and the fear of coronary constriction, been demonstrated to be a contraindication to the use of digitalis. Some basis for such apprehension was afforded by observations of Gilbert and Fenn[102] on cases in which administration of digitalis was followed by appearance or intensification of cardiac pain. They attribute the pain to coronary constriction. However, the effect of digitalis on coronary flow is complex and not entirely elucidated, and it is conceivable that when digitalis increases cardiac output it may augment coronary flow. In an investigation of 120 patients with cardiac pain due to arteriosclerotic heart disease, Gold[103] *et al.* arrived at the conclusion that "in cases of angina pectoris without congestion the likelihood is negligible that the use of digitalis will, by a direct action on the circulation, increase or diminish cardiac pain." It is a common observation that when patients with coronary arteriosclerosis or aortic regurgitation and angina pectoris develop failure of the right side of the heart, the cardiac pain lessens or disappears; patients on the ward who are in right-sided failure almost never require nitroglycerin. Among the factors involved may be lessened activity and increased pressure in the coronary veins. It is therefore possible that when cardiac pain develops after the administration of digitalis—I have observed this in exceptional cases—it is due to greater activity following improvement in the functional capacity of the heart or decrease in pressure in the coronary veins, and not to coronary constriction.

There would, therefore, seem to be no valid objection to the use of digitalis in the heart failure of hypertension, unless it is contraindicated by an arrhythmia, and in actual practice the results are often definitely beneficial. As in heart failure of rheumatic etiology, the most spectacular results are usually obtained when auricular fibrillation with rapid ventricular rate is present, but even with sinus rhythm the administration of digitalis often produces rapid and striking improvement. It is no longer necessary to emphasize that, as long ago demonstrated by Harrison[104] and his associates, digitalis is often of great value in the isolated left ventricular failure of hypertension, in which exertional or paroxysmal dyspnea, cough or weakness may be the only symptoms and engorgement is confined to the lesser circulation. Digitalization of such patients is often followed by prompt improvement, indeed, such improvement may be the strongest evidence of the pathogenesis of their symptoms. Hypertensives who have recovered from heart failure are always in dange
tained on digitalis. The technique of
patients and will not be discussed here
that the dose of digitalis may be affected by renal insufficiency.

Mercurial Diuretics.—Probably the greatest advance ever made in the treatment of heart failure in essential hypertension was the introduction of the mercurial diuretics. They are more often helpful than is digitalis and their use in combination with salt restriction and digitalis has greatly prolonged the life span of most hypertensive patients after the heart has first given way. By the aid of mercurial diuretics, many patients with

hypertensive and arteriosclerotic heart disease are given years of happy ... would formerly have been denied them. Mer-

characterized only by dyspnea. The technique, ... complications of the use of mercurial diuretics have been discussed in

mercurials as an adjuvant to dietary sodium restriction.

with hypertensive and arteriosclerotic heart disease and can be avoided only by careful selection and supervision of patients treated by dehydration. With increasing frequency in recent years, I have witnessed the development of renal insufficiency with azotemia in individuals with chronic

treated for months or years with no symptoms other than those resulting from heart failure and a normal nonprotein nitrogen level in the blood. Then, often coinciding with improvement in congestive manifestations (disappearance of dyspnea, edema, congestive râles and enlargement of the liver), there develop such symptoms as weakness, nausea, vomiting, drowsiness or restlessness, and often disorientation. Examination reveals

ia and usually hypo-

the dominant features

to those of renal insufficiency. This clinical picture is the one which Schroeder[108] described so well under the name of the *low-salt syndrome*. With administration of sodium chloride (or sodium lactate or bicarbonate if acidosis is pronounced) and withdrawal of the mercurial diuretic, the renal insufficiency may improve, in other and not rare cases, the failure of the kidneys leads to a fatal outcome. At necropsy, the kidneys reveal only regressive and necrotizing changes in the tubular epithelia, the parts of the tubules involved remain to be established.

Such cases were rare twenty years ago, but they have become more common in the past few years. This increase in frequency has coincided with the popularization of the treatment of heart failure by intensive dehydration through sodium restriction and frequent

... salts, and since the syndrome occurs in patients who have been given ample water (Schemm regimen) and ammonium chloride to potentiate the mercurial, the evidence seems strong

that the renal failure is the result of sodium deplet...
connection ...
elucidated.
and necrops... ...epithelia,
which have ... gone on to patchy necrosis. The most probable mechanism of the renal damage would seem to be that as a result of dietary restriction of sodium and mercurial diuresis extracellular and plasma volumes are lowered below their previous values with resultant decrease in renal blood flow and ischemic damage to the renal epithelia. This apparently occurs only if the kidneys are arteriosclerotic or arteriolosclerotic, for renal insufficiency complicates the dehydration treatment of cardiac failure almost exclusively in hypertensive and arteriosclerotic heart disease and is extremely rare in the rheumatic heart. Another factor that probably participates in producing the sodium depletion is defective sodium conservation by the damaged kidney so that a "salt-losing" kidney develops. It is possible, but requires demonstration, that there may be an element of mercurial poisoning in damage to renal epithelia rendered more susceptible to such poisoning by ischemia.

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by azotemia (NPN above 45 mg. per cent) It is neglect of these precautions which leads to most instances of iatrogenic sodium depletion in essential hypertension.

Attacks of *cardiac asthma* due to paroxysmal left ventricular failure are a common and usually nocturnal emergency in essential hypertension. Especially in elderly patients and in initial attacks, one should consider the possibility that the seizure is due to myocardial infarction In attacks not due to myocardial infarction, the blood pressure usually rises at the onset, but the same may occur briefly in myocardial infarction, although then the pressure has usually fallen by the time the physician arrives The attacks can usually be prevented by salt restriction, periodic mercurial diuresis and digitalization Patients subject to the attacks should have their main meal at midday and eat a light dinner. Diminution of the venous return by sleeping with the head of the bed elevated may help, using several pillows is not as efficient Morphine is the sovereign remedy; a quarter grain should be given immediately and repeated in twenty minutes if necessary. The action of morphine is so specific and so often followed by rapid clearing of pulmonary engorgement that it would appear, in addition to allaying apprehension, in some way to diminish venous return to the heart Oxygen is to be given if the attack is not quickly relieved. Should the patient not have taken digitalis, he is to be digitalized by intravenous injection of 1.6 mg of Lanatoside C. A mercurial diuretic should be given intramuscularly. If the pulmonary edema becomes menacing with rise in blood pressure, phlebotomy is called for. Positive pressure respiration may help in clearing pulmonary edema (Barach[108] *et al.*). However, it should not be used where there is shock (*e. g.*, in myo-

cardial infarction) because it lessens venous return to the heart. Recently, Luisada ... inhalation of alcohol vapor of help in the treatment of ... edema. It functions as an antif...

... It seems to ...

Angina Pectoris and Myocardial ... Nitroglycerin is just as effective ... the indications for ...

there is cerebral hemorrhage

... by caloric restriction is often of great ... be desired to give small ...

in combination with a barbiturate ...

weight reduction suffices to alleviate dyspnea

Blumgart[109] and his coworkers have obtained excellent results in many cases of both angina pectoris and heart failure by production of hypothyroidism with radio-iodine. The place of this method of treatment in ... heart disease remains to be determined

... gives the central therapeutic ...

lesional nature. Many of the patients ... state with variegated and seemingly hypochondriacal complaints ... difficult to control. Not rarely these symptoms are iatrogenic and date ... high blood pressure. The most important ... elimination of ...

in practice), and various types of ... carried out by the family physician. A vacation is often of great avail in overworked or overworried individuals, but one must guard against engendering hypochondriasis. Mild sedatives such as phenobarbital or chloral hydrate, which can be continued over long periods of time, are often valuable therapeutic accessories, bromides should not be given to ... common complaint, reassurance ...

Especially when there is ... heart," advice to take such exercise as golf or walking may be of notable help.

Headache may be difficult to control. For therapy, it is necessary to differentiate in hypertensives at least the following varieties: headache due to mental tension, sinusitis or other cause unrelated to the high blood pressure, true migraine, often characterized as such by the history and symptomatology and which usually responds to ergotamine, headache due

to the hypertension, as may be proved by disappearance when the blood pressure is lowered; headache due to increased intracranial pressure resulting from edema of the brain in the malignant phase of essential hypertension; and headache due to cerebral arteriosclerosis and its complications, hemorrhage and thrombosis.

In headaches due to hypertension, the primary indication is of course to attempt to lower the blood pressure. The available measures—reassurance, rest, sodium restriction, antihypertensive drugs and sympathectomy—are discussed elsewhere in this chapter. However, analgesics such as aspirin, acetphenetedin, aminopyrin, codein and Demerol are often needed. The common type of hypertensive headache which awakens the patient early in the morning and improves after he gets up and about is sometimes prevented by elevating the head of the bed 18 inches with blocks. Extremely severe headache in plethoric hypertensives may be relieved by phlebotomy. Prompt relief of very severe hypertensive headache may be obtained by cautious parenteral injection of alkavervir (page 875) or hexamethonium (page 877).

Perhaps the most severe headache in essential hypertension is that in which the cephalalgia is a manifestation of increased intracranial pressure also evidenced by papilledema and high spinal fluid pressure. The headache may be accompanied by nausea and vomiting. This occurs in the malignant phase of essential hypertension and is due to edema of the brain. At times *lumbar puncture* affords temporary relief. Very often it fails ignominiously. Indeed, following a detailed investigation of the subject, Shelburne[110] *et al.* incline to the opinion that lumbar puncture for the relief of hypertensive headache is not justified In these cases with an edematous brain and high spinal fluid pressure, the fluid must be removed very slowly and the pressure not brought down quite to normal levels; otherwise, there may be severe and even fatal reaction, perhaps as a result of herniation of the swollen brain into the foramen magnum Spectacularly favorable results may be obtained by the *very cautious* parenteral injection of alkavervir or hexamethonium (pages 875,877), at present this appears to be the method of choice, but more experience is required to learn whether an abrupt fall in blood pressure is ever dangerous when intracranial pressure is elevated by cerebral edema. Parenteral injection of magnesium sulfate (page 362) or intravenous administration of 100 cc of 50 per cent sucrose solution sometimes help, but are not nearly as effective as alkavervir or hexamethonium and sucrose may not be without danger to the kidneys. In instances of the malignant phase of essential hypertension in which the symptoms of increased intracranial pressure completely dominate the clinical picture, as they may for weeks or even months so that brain tumor is simulated, *subtemporal decompression* has been performed. This operation is to be considered especially when the choked disc is leading to rapidly progressive loss of vision In several such cases, including two that I observed, great symptomatic improvement, sometimes with restoration of vision, has followed (see page 363 for references).

The treatment of *convulsions* and other manifestations of *hypertensive encephalopathy* is considered in Chapter 11.

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severely impaired That sodium restriction sympathectomy carry with them great dangers in patients with badly impaired renal function is pointed out in the sections on these modalities of treatment

hypertensives stand operations quite

failure or coronary insufficiency, suffered cerebral vascular accidents, the risk of operation is considerably increased In such individuals the necessity for operation should be carefully weighed against the augmented risk With severe impairment of renal function and especially when decompensation of the kidney is attested by azotemia, the risk of aggravation of the renal insufficiency by the d renal blood flow incident to anesthesia and operation is very

both improvement in renal function and decrease in blood pressure. In

all operations on hypertensives, the anesthetist should make especial efforts to avoid tissue anoxia.

Diabetes Mellitus.—Essential hypertension and diabetes often coexist. The diabetes is managed much as when it occurs in individuals with normal blood pressure. It is to be borne in mind that with functionally impaired kidneys the blood sugar may be very high with little or no glucose in the urine. Most of the cases are mild and readily controlled by diet, but extremely severe diabetes may also complicate essential hypertension. The antidiabetic diet with its frequent slight undernutrition is excellently

produced with its resultant pressor effect.
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hypertension and diabetes often have severe peripheral arteriosclerosis and are to be warned about the dangers of slight injuries or infections of the feet.

Syphilis.—The technique of antiluetic treatment is not altered by the existence of uncomplicated essential hypertension. Well-marked impairment of renal function, as revealed by hyposthenuria, contraindicates the use of mercury, arsenic or bismuth; even iodides are to be given cautiously because of the readiness with which manifestations of iodism appear. I have twice seen deaths from mercurial colitis and once from arsphenamine hepatitis and dermatitis in such cases. Under these circumstances antiluetic treatment should generally be confined to penicillin. If the hypertension is complicated by coronary insufficiency, or if essential hypertension and luetic aortitis coexist, antisyphilitic treatment should be inaugurated gingerly and pursued with great caution because of the danger of

lower arterial tension Bain[112] *et al.* found slight but definite reduction in both systolic and diastolic pressures following the high frequency current, and slight diminution in systolic pressure after diathermy. Humphries[113] also reported good results from diathermy in high blood pressure But it seems improbable that these effects are considerable enough to be of real aid in the treatment of essential hypertension. Sweating procedures are often prescribed for hypertensive individuals in the "health gymnasiums" often patronized by business men. However, Gibbons and Chapman[113] found that dehydration by sweating, unaccompanied by loss of much electrolyte, has no lasting effect on the blood pressure of hypertensives. It appears that any effect these physiotherapeutic measures may have in hypertensive disease is purely through suggestion.

Tirala[114] and Rappaport[115] have reported favorable results in essential hypertension from hyperventilation by systematic deep breathing exercises, but give few details (see also the work of Raab, page 732). I have tried the method in a few cases and occasionally observed some transitory lowering of blood pressure, but the general condition of the patients was

not sensibly altered. Inhalation of oxygen has also been recommended, but I have no experience with this method of treatment, which has no rationale.

Phlebotomy.—The blood pressure is not notably lowered by the abstraction of such volumes of blood as can be removed for therapeutic purposes. Worm-Mueller[116] long ago showed that in the dog the removal of from one-fifth to [illegible] table depress [illegible] level [illegible] equally slight. Thus, Miller[117] found that in 4 patients with hypertension, removal of 500 cc of blood caused a maximum fall in blood pressure of only 15 mm. Rarely, very much greater drops than this are encountered, while in other cases measurement a few minutes after the phlebotomy reveals no change in blood pressure; the blood pressure is made up too quickly by the inflow of tissue fluid.

From these facts, it is clear that venesection is of little or no use as a means of lowering arterial tension. Nevertheless, it is a valuable thera- [illegible]

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all operations on hypertensives, the anesthetist should make especial efforts to avoid tissue anoxia.

Diabetes Mellitus.—Essential hypertension and diabetes often coexist. The diabetes is managed much as when it occurs in individuals with normal blood pressure. It is to be borne in mind that with functionally impaired kidneys the blood sugar may be very high with little or no glucose in the urine. Most of the cases are mild and readily controlled by diet, but extremely severe diabetes may also complicate essential hypertension. The antidiabetic diet with its frequent slight undernutrition is excellently adapted to the hypertension. Sodium restriction is well tolerated by diabetics. If necessary insulin is to be used; it does not affect the blood pressure (contrary to older claims cited in previous editions) unless hypoglycemia is produced with its resultant pressor effect. When insulin is given to patients with coronary insufficiency care must be taken to avoid hypoglycemia because of the danger of precipitating anginal attacks. Patients with both hypertension and diabetes often have severe peripheral arteriosclerosis and are to be warned about the dangers of slight injuries or infections of the feet.

Syphilis.—The technique of antiluetic treatment is not altered by the existence of uncomplicated essential hypertension. Well-marked impairment of renal function, as revealed by hyposthenuria, contraindicates the use of mercury,

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hepatitis and dermatitis in such cases. Under these circumstances antiluetic treatment should generally be confined to penicillin If the hypertension is complicated by coronary insufficiency, or if essential hypertension and luetic aortitis coexist, antisyphilitic treatment should be inaugurated gingerly and pursued with great caution because of the danger of menacing or even fatal reactions

Physiotherapy.—Such physiotherapeutic measures as the high frequency current, diathermy and sweating procedures have been used in the effort to lower arterial tension. Bain[112] *et al* found slight but definite reduction in both systolic and diastolic pressures following the high frequency current, and slight diminution in systolic pressure after diathermy. Humphries[113] also reported good results from diathermy in high blood pressure. But it seems improbable that these effects are considerable enough to be of real aid in the treatment of essential hypertension. Sweating procedures are often prescribed for hypertensive individuals in the "health gymnasiums" often patronized by business men. However, Gibbons and Chapman[116] found that dehydration by sweating, unaccompanied by loss of much electrolyte, has no lasting effect on the blood pressure of hypertensives. It appears that any effect these physiotherapeutic measures may have in hypertensive disease is purely through suggestion.

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2. Denervation, partial resection or, more recently, total ablation of the adrenals.
3. Attempts to increase renal blood flow by denervation or production

Of these operations, only extensive sympathectomy ...
Partial adrenalectomy is carried out but rarely and then in association with extensive sympathectomy (apart, of course, from hypertension in the Cushing syndrome). Total adrenalectomy with or without sympathectomy is as yet in the investigative stage. The operations on the kidney are now only of historical interest. Only a few operations on the frontal lobe have been carried out

EXTENSIVE SYMPATHECTOMY

Interruption of sympathetic pathways for the relief of high blood pressure was suggested by Bruening[2] (cf. Martin[3] for the early history). However, the actual inauguration of sympathetic surgery for hypertension is due to Rowntree and Adson.[4] In 1925 they reported resection of the

denervate enough arteries Subsequently, more extensive sympathectomies were devised by Adson,[5] Peet,[6] Smithwick[7] and others. These will be discussed below

So great differences by the cognoscente after so many years are strong indications that—while the operation is still advisable *faute de mieux* in some cases—it is far from a sovereign remedy

Rationale of Sympathectomy.—The pioneer operations at the Mayo Clinic were motivated by observation of increased blood flow through the extremities of patients with vasospastic disease following sympathetic ganglionectomy and trunk resection, and of increase in the caliber of the retinal arteries and veins after cervicothoracic ganglionectomy (Craig and Brown[8])

In accord with this line of thought, subsequent investigations have shown that *the lowering of blood pressure by extensive sympathectomy is actually due to decrease in peripheral resistance.* This is proved by the findings that, in patients in whom sympathectomy has lowered the resting blood pressure in the ...

This diminution in peripheral resistance is doubtless due to dilatation of small blood vessels in extensive territories While it is known that the vessels of the extremities and brain (pages 301 and 302) are constricted in

Chapter

30

ESSENTIAL HYPERTENSION: VII. SURGICAL TREATMENT

The past two decades have witnessed the introduction of several varieties of surgical treatment of essential hypertension. Because of our ignorance of the ultimate causes of essential hypertension, these procedures have mostly been intended to interrupt one or another link in the effector mechanism by which the blood pressure is elevated.

Such a line of attack has not seemed rational to all. It has been suggested that, if the elevation of blood pressure subserves the salutary purpose of maintaining blood flow through the kidney or another organ with narrowed arteries or arterioles, fall in arterial tension may entail inadequate perfusion of the organ in question. Plausible as this suggestion seems, *a priori*, it lacks tangible support. On the contrary, Page[1] showed that the urea clearance of patients with essential hypertension is not affected by fall in arterial pressure, whether spontaneous or induced by the administration of sodium thiocyanate or the injection of colloidal sulfur. It has also been found that when blood pressure in essential hypertension is lowered by the surgical operations to be described or such a drug as hexamethonium, renal function does not suffer and there is no evidence of deficient blood flow through other organs.* Of course, these findings do not necessarily speak against the "compensatory" nature of hypertension; it is readily conceivable that the operation or drugs that lower the blood pressure do so by alleviating vasoconstriction in the kidney or another organ that originally called forth the hypertension, thus removing the necessity for the generalized arteriolar constriction which is the immediate mechanism of the elevation in blood pressure.

The individual forms of surgical treatment of essential hypertension have been corollaries of corresponding theories of the mechanism of elevation of blood pressure. Four general groups of procedures have been tried:

1. Extensive sympathectomy, with the object of interrupting vasoconstrictor impulses to large territories, notably the splanchnic area.

* An exception is constituted by patients with marked arteriosclerosis in some organ. In them, fall in blood pressure—as a result of hexamethonium, for example—may result [illegible]
with [illegible]
or my[illegible]
may develop.

In hypertensive patients who suffer a myocardial infarction, the blood pressure may remain for years 50 mm. or more lower than its previous level. Nevertheless, renal function is rarely affected after the initial stages of the infarction The nature of the adjustments in renal hemodynamics under these circumstances have not been unraveled.

Sympathectomy is not a causal treatment. ...
... long as increased tone of the sympathetic

... thectomy is other than the induction of ...

such fall in blood pressure as follows the operation gradually ... disappears in the large majority of instances. Two to five years after sympathectomy, Mendlowitz and Touroff's measurements of blood flow through the toes before and after heat plus tetraethylammonium chloride showed the presence of sympathetic tone in every case. One factor in this return of sympathetic tone has been thought to be regeneration of sympathetic fibers. However, in 2 cases Dember[21] found practically no regeneration of nerve fibers in the adrenal gland after sympathectomy. Mendlowitz and Touroff[22] also consider the possibility that ganglion cells whose fibers are not severed may assume vasoconstrictor function (Randall[23] *et al.*). Moreover, Mendlowitz and Touroff's observations show that after sympathetic vasoconstrictor tone is diminished by sympathectomy, there is a

... was mentioned that ... consisted in the resection of the second, third and fourth lumbar sympathetic ganglia with their intervening trunks. Since this proved inadequate, subsequent operators denervated more extensive vascular territories, always including the splanchnic area.

Section of Anterior Spinal Roots.—This operation was introduced by Adson and Brown, who performed bilateral section of the anterior roots from the sixth thoracic to the second lumbar segments inclusive. They hoped that this procedure would lower arterial pressure not only through denervating the arterioles in the splanchnic area, but also by denervating the adrenals and as a result of the fall in intra-abdominal tension due to paralysis of the muscles of the abdominal wall. Some favorable results—including significant lowering of blood pressure, disappearance of headache, clearing of retinopathy and other symptomatic improvement—were obtained with this operation by Adson and Brown and Page and Heuer.[24] However, the procedure is a formidable one involving laminectomy, the operative mortality is higher than with other forms of sympathectomy, the paralysis of the abdominal wall and other side-effects are very distressing, and the results are not superior to those of splanchnicectomy. Anterior root section has therefore been abandoned.

pr

essential hypertension quite as much as those of the splanchnic area, nevertheless the latter would appear to be quantitatively especially important in the effects of extensive sympathectomy.

Splanchnic Vasodilatation.—Splanchnic denervation has been included in all extensive sympathectomies on the basis, well supported by the data of experimental physiology, that splanchnic constriction plays an important part in any pressor mechanism. Wilkins[13] and his coworkers found that six or eight months after operation, whether or not the resting blood pressure was much changed, hepatic blood flow in the horizontal position had resumed its preoperative value; this indicates that the changes in blood pressure occur *pari passu* with corresponding alterations in the state of constriction of the splanchnic vessels. Wilkins *et al.* also showed that the constriction of the splanchnic vessels and resultant decrease in portal-hepatic blood flow which occur in normals and hypertensives on assumption of the erect posture do not take place after splanchnicectomy. It thus appears that dilatation of the splanchnic vessels plays an important part in the hypotensive effect of extensive sympathectomy.

Orthostatic Hypotension.—Most patients who have undergone extensive sympathectomy have orthostatic hypotension for months after operation; it may last, usually in small degree, for years. The degree of orthostatic hypotension generally parallels the extent of the denervation; it is slight after supradiaphragmatic sympathectomy and severe after subtotal sympathectomy. The orthostatic hypotension is due to the pooling of blood in the dependent parts of the body. When orthostatic hypotension is present, it may well play a part in relief of headache and heart failure, for it lowers the venous return to the heart and average arterial pressure during part of the day. However, orthostatic hypotension is not the complete explanation of the favorable effects of sympathectomy, for in successful cases the blood pressure in the horizontal position is also depressed and this lowering may persist after the postural fall has disappeared.

Inhibition of Pressor Reflexes.—It is possible that sympathectomy may also help through prevention of superelevations of blood pressure in response to emotional and other pressor stimuli Wilkins[14] *et al.* have shown that the overshoots of blood pressure which follow the Valsalva maneuver by hypertensive patients are not present after sympathectomy. Such inhibitions of pressor responses may occur even when the operation has not lowered the resting level; Wilkins[15] has observed the suppression of pressor responses as long as nine years after operation. Smithwick found that the cold pressor response (page 764) is diminished after sympathectomy, especially in the erect posture, but this diminution was not definite in Bechgaard and Hammarstroem's[16] observations with the patients in bed

Relief of Renal Ischemia.—Early suggestions by Peet and others that sympathectomy lowers blood pressure by augmenting renal blood flow have been disproved by the finding that it is unaltered by the operation (Corcoran and Page,[17] Foa[18] *et al.*). Experimental renal hypertension is unaffected by sympathectomy (page 321).

From the foregoing, it would appear that when sympathectomy lowers the blood pressure, the quantitatively predominant element is splanchnic vasodilatation. The associated orthostatic hypotension and inhibition of

the follov ... years after operation, the following were the findings: ... cent; 95 ... cardiac, .. patients had normal blood pressure; of the 112 patients with malignant hypertension (papilledema 1 diopter or more), 19 per cent were alive.

In the last report of the late Dr. Max Peet, who rendered such signal services in the surgical treatment of essential hypertension, he stated that the blood pressure was significantly reduced 5 to 12 years after supra-

it is completed at one s ... two weeks after operati ... and orthostatic hypote

wick found that supradiaphragmatic sympathectomy failed to have a significant effect on the blood pressure in a single one; there was a significant effect on the blood pressure in 5 of 13 patients with Group I eye grounds and in 1 of 19 with Group II eye grounds. Page and Heuer,[24] Ayman and Goldshine,[27] and others have also found that the proportion of

one has maintained a normal blood pressure for over ten years. In some of these, hypertensive retinopathy cleared up. But in the vast majority of the patients, the results of the operation did not appear to me worthwhile. Even in those who seemed ideal for the operation, a worthwhile result could not be confidently predicted. Thus, during the early days of enthusiasm for supradiaphragmatic sympathectomy, I recommended the operation in a sixteen-year-old yout ... pressure usually 180/120 mm.) wh ... examination two years previously ... the blood pressure was unaf-

... hnique for extensive sympa- ... was developed by Smithwick and is now generally used. The results he obtained with either supra- or infradiaphragmatic sympathectomy were unsatisfactory. He found, however, that in some patients who had not responded to supradiaphragmatic sympathectomy the extension of the denervation that was rendered pos-

had performed celiac ganglionectomy. Crile regarded essential hypertension as an expression of hyperactivity of a part of the sympathetic nervous system. He found the celiac ganglia and the connecting nerve [illegible]

in patients in all stages of essential hypertension symptomatic relief had been obtained by 87 per cent and the blood pressure had been reduced to normal in 17 per cent. Crile's work attracted much attention at the time, but it was not adequately controlled and the results have not been confirmed. White and Smithwick[26] point out that celiac ganglionectomy does not completely denervate the splanchnic bed and has the theoretical shortcoming that, being predominantly a postganglionic resection, it may sensitize the vessels to stimulation by epinephrine and other humoral pressor agents.* In several patients with essential hypertension in whom celiac ganglionectomy had been performed, and whom I followed, the results were unsatisfactory. The operation has been abandoned.

Infradiaphragmatic Sympathectomy.—This operation was developed by Adson, Allen and their coworkers. Through a lumbar approach, they perform bilateral resection of the splanchnic nerves, celiac ganglia and upper two lumbar ganglia. The operation is carried out first on one side and then after an interval of about ten days on the opposite side. At first, they combined the foregoing with partial adrenalectomy, but this seemed not to improve the results.

An advantage of infradiaphragmatic sympathectomy is its very low operative mortality; Adson and his associates performed the operation in 158 patients with essential hypertension without an operative death. In a small proportion of patients with severe forms of essential hypertension, worthwhile lowering of the blood pressure results Much more often, however, the results of the operation are not strikingly beneficial. It appears that with an infradiaphragmatic approach the denervation of the splanchnic vascular bed is not as extensive as that attained with supradiaphragmatic operations. For this reason, exclusively infradiaphragmatic sympathectomy has been abandoned in recent years. Details of the results may be obtained from the original papers of Adson and his associates and, in brief outline, in the fourth edition of this book.

Supradiaphragmatic Sympathectomy—This operation was introduced in 1933 by Peet; by 1945 he had operated on 1500 hypertensives It consists in bilateral supradiaphragmatic resection of a 9 to 13 cm long segment of the major and minor splanchnic nerves as well as the tenth, eleventh and twelfth dorsal sympathetic ganglions. This is accomplished through bilateral paravertebral incisions with resection of a segment of the eleventh rib on each side. Peet and Isberg reported the results of supradiaphragmatic sympathectomy on 437 patients with essential hypertension who had been operated from five to twelve years previously. Of these patients 82 per cent had "serious organic disease" prior to operation. At the time of

* However, Duff[27] has recently demonstrated increased sensitivity to epinephrine of vessels sympathectomized either by preganglionic section or ganglionectomy.

Sympathectomy Only a Palliative Procedure.—There are many patients with severe essential hypertension in whom sympathectomy produces brilliant results, which both the patient and physician agree are decidedly worthwhile. Unfortunately, however, there are also many cases in which the results of the operation are not commensurate with the suffering entailed and in which, with hindsight, both patient and physician wish the

it is borne in mind that *the operation constitutes merely a palliative and not a causal or curative treatment.* The writer has not seen any patient with essential hypertension whom he regarded as cured by sympathectomy in the

cardiac output and the adaptation of the circulation to the erect posture;

anticipa-

operation.

ations and

such protean

ve that a non-

large series of

cases of Peet, Smithwick, and Bechgaard and Hammarstroem, in which clinically similar groups of operated and nonoperated cases were compared after periods of more than ten years, show definitely that the average survival period of the operative cases is greater

Much the most extensive, protracted and well-controlled studies of the effects of thoracolumbar sympathectomy are those of Smithwick, the father of the operation By late in 1951, he had operated on about 2000 patients and was able to report on the first 892 of these, who had been followed between four and twelve years after operation The results in these cases were compared with those in 411 treated nonsurgically and followed for a corresponding period of time Following the ophthalmoscopic criteria of Keith *et al* (page 812), the cases were classified into four groups. In each of these four groups, the mortality was much less for those who had been

in Group IV (essential

d by papilledema) In

a scoring system which takes into consideration the arterial damage in the heart, brain, kidneys and retina. His findings indicate that thoracolumbar sympathectomy improv

d

to the arteries and those in whom the arterial injury is far advanced Peet had also previously shown on his very extensive material followed for over ten years that the mortality rates in the

sible by an additional infradiaphragmatic approach produced orthostatic hypotension, which had not developed after the first operation, and sometimes also lowering of the blood pressure in the horizontal position. Smithwick performs his operation in two stages; the second side is operated, if all goes well, about ten days after the first. He carries out the procedure by a retropleural, transdiaphragmatic, retroperitoneal approach involving resection of the twelfth rib Usually, the sympathetic chain from above [illegible]

[illegible] the sympathectomy may be carried further up and/or down. Largely with the object of removing the upper dorsal ganglia, the operation has also been performed by a transthoracic exposure; Smithwick states that the transthoracic approach augments morbidity and mortality and this has been decidedly true in the cases observed by the writer.

Subtotal Sympathectomy.—By extending the Smithwick operation upward to include the stellate ganglion, an approach to total sympathectomy is attained. The chief advocate of this operation has been Grimson[28] His operation consists in resection of the entire thoracic sympathetic chain, the splanchnic nerves, the celiac ganglia, and part or all of the lumbar sympathetic chains This formidable procedure is performed transthoracically in two stages two or three weeks apart Grimson found that in experimental neurogenic hypertension in the dog due to increased intracranial pressure or section of the moderator nerves, total sympathectomy lowered the blood pressure but partial did not. But, as pointed out by Bechgaard and Hammarstroem, this observation has no bearing on the problem of human ess [illegible]

to [illegible]

pre [illegible]

nev [illegible]

for essential hypertension since it effects the maximal denervation. Eighteen to seventy-six months after subtotal sympathectomy in 41 patients with essential hypertension, Grimson observed objective improvement in 76 per cent and symptomatic improvement in 79 per cent, 9 had a blood pressure below 150/100 mm. However, it does not seem to have been demonstrated that the effect of subtotal sympathectomy on the blood pressure and subjective manifestations in essential hypertension is superior to that of the Smithwick operation. The operation is a very formidable one which usually entails protracted convalescence, probably has greater mortality (*cf.* Hinton and Lord[29]) and produces Horner's syndrome. Smithwick has carried out subtotal sympathectomy in 16 cases; 4 of the patients suffered prolonged total disability because the interruption of both the splanchnic vasoconstrictor and cardioaccelerator mechanisms resulted in orthostatic hypotension for which the patients were unable to compensate by acceleration of the heart He does not regard total sympathectomy as indicated. The writer has had no experience with the operation.

At present, Smithwick's thoracolumbar sympathectomy is the form of extensive sympathectomy used in the vast majority of instances in this country. The following discussion refers largely to this operation.

Results at Successive Periods after Sympathectomy

Time After Operation (Months)	Patients				
13–24	40	10	13	22	10*
25–48	48	6	12	24	6
49–72	18	6	7	12	1
72 plus	3			1	1

* These 10 deaths occurred in the first twenty-four months (6 in the first year); they do not include 4 operative deaths.

At the last measur
below the preoperativ
pressure had fallen si
pressure reading was

The most striking effect on the blood pressure was in the following case:

A man of thirty-six years was known for three years to have essential hypertension. He had severe occipital headaches during this period. Preoperative blood pressure averaged 200 mm systolic and 135 mm. diastolic, he had narrowed retinal arterioles with arteriovenous compression He underwent thoracolumbar sympathectomy in December, 1941. He felt entirely well after recuperating from the operation and worked hard In October, 1947, his blood pressure was 116 mm. systolic and 75 mm diastolic. I was informed in January, 1950, that his blood pressure was 125/90 mm.

It will be noted that in each age group the blood pressure averages lower than the preoperative level. The 119 patients had an average preoperative blood pressur
examination,
age blood pr
was thus an
pressure of 13 per cent

While the natural history of essential hypertension is characterized by pronounced fluctuations in blood pressure, the tension in untreated patients usually does not tend to fall over a protracted period unless there is

after surgery is the result of the sympathectomy.

In very many patients the blood pressure falls close to normal for a postoperative period of weeks or a few months This interval is too brief to be of much significance, and indeed a similar transitory fall is not rare after any operation, it is not included in the tables. Most often the pressure than gradually rises However, in some the pressure has remained below 150 mm systolic and 100 mm. diastolic for periods of observation up to almost six years. In interpreting the relatively high proportion of such satisfactory pressure levels in the group followed for between forty-

different groups of hypertensives are lessened by supradiaphragmatic sympathectomy.

Bechgaard and Hammarstroem compared in various details the results in operated and nonoperated hypertensives divided into four groups according to the severity of the process. They found the prognosis better in the operated cases in all four groups; the difference was very significant in the two worst groups.

These findings leave no doubt that in some patients with essential hypertension life is prolonged by sympathectomy. My experience has been the same. Particularly convincing to me have been the patients with severe retinopathy who improved for five or more years following sympathectomy; such a course of events is *extremely* rare in the spontaneous course of essential hypertension.

Effect of Sympathectomy on the Blood Pressure.—The effect of sympathectomy on the blood pressure is exemplified by the findings in 119 patients with essential hypertension in whom I recommended the operation. The latter was carried out by different surgeons, after which I was able to study the patient. The indications and contraindications used in the selection of the patients were essentially the same as those described below (*cf.* Fishberg[30]). Two of the patients had Adson's *infradiaphragmatic* sympathectomy, 8 Peet's supradiaphragmatic operation, and 109 Smithwick's thoracolumbar sympathectomy. Some of the results are summarized in the following two tables; others are discussed below:

RESULTS OF SYMPATHECTOMY IN ESSENTIAL HYPERTENSION (Fishberg[30])

Age	20–29	30–39	40–49	50–55	*Total*
Patients	8	40	66	5	119
Follow-up (months)					
Average	40	34	30	35	32
13–24	1	10	28	1	40
25–48	4	19	22	3	48
49–72	3	7	7	1	18
Over 72		2	1		3
Operative Deaths			4		4
Later Deaths		8	10		18
Average Preoperative Blood Pressure	196/129	214/137	220/134	228/133	218/135
Average Postoperative Blood Pressure*	156/106	188/121	183/119	180 111	184/118
Blood Pressure Under 150/100*	1	9	11	1	22
Systolic Blood Pressure 25% Lower*	2	12	22	2	38
Diastolic Blood Pressure 25% Lower*	3	12	16	1	32
Systolic Blood Pressure Higher*	1	4	10	1	16
Diastolic Blood Pressure Higher*	1	8	11	1	21
Worthwhile Symptomatic Improvement*	4	23	29	3	59

* Findings at the last examination. Blood pressure measured in the reclining position.

vasoconstriction in the upper parts of the body may aid in regulating body temperature by counteracting the increased heat loss due to dilatation in the lower extremities

The Heart.—As would be anticipated, if sympathectomy produces a significant and protracted lowering of elevated blood pressure, cardiac enlargement due to the hypertension may recede. *This was first detected* by Braden and Kahn[33] in patients who had undergone supradiaphragmatic sympathectomy. The enlarged heart may diminish in size, the rotation of the electrical axis to the left may lessen, and the electrocardiographic manifestations of left ventricular strain may disappear. *The latter improvement* may include elevation of a depressed RS-T junction and segment to the isoelectric and return of an inverted T wave *to the upright* configuration. Isberg and Peet[34] found that of 384 patients still alive five

in size Similarly, Canabal[35] *et al* found that while in 50 nonoperated hypertensives followed for an average of eight years only 5 per cent had even questionable improvement in the electrocardiogram, the latter improved in 57 5 per cent of patients who had undergone dorsolumbar sympathectomy But if the cardiac enlargement is very marked, it apparently is little affected by sympathectomy, this is indicated by Isberg and Peet's finding that when the frontal area or transverse diameter was more than 50 per cent above the predicted normal, splanchnic section was of no avail Regression of cardiac enlargement has been observed only when sympathectomy has produced protracted lowering of blood pressure.

It goes without saying that improvement seems possible following sympathectomy of only such part of cardiac enlargement and electrographic abnormality as is due to elevated blood pressure and not to the ischemic muscle damage of coronary narrowing.

I have had little experience with the effects of sympathectomy on congestive failure, cardiac arrhythmias and angina pectoris in essential hypertension because I have regarded these as contraindications to operation. Others have described some results which they regarded as worthwhile in

Isberg and Peet report the operated hypertensive alization has 1 chance in 11 hypertensives who had a coronary occlusion were still alive five to nine years after sympathectomy Chavez ar nent of hypertensive patients ope fact, they believe that intractable may be an indication for sympathectomy provided th

the heart and avoid excessive postural hypotension and tachycardia Gallop rhythm which persists despite bed rest, sodium restriction, digitalization and mercurial diuresis may disappear after sympathectomy

nine and seventy-two months, it should be borne in mind that 20 patients—including those responding least well to sympathectomy—had succumbed at earlier periods. Moreover, 2 of these patients had had myocardial infarction long after the operation, which presumably participated in keeping the blood pressure down.

These observations are not very different from those made by Palmer[31] and by Evelyn[32] *et al.* Palmer found that three to five years after sympathectomy about 25 per cent of the patients have a blood pressure less than 150/110 mm. In a careful follow-up of 100 patients five years after sympathectomy, Evelyn *et al.* observed that the blood pressure was normal in 8 per cent and significantly reduced in an additional 13 per cent.

Orthostatic Hypotension.—The vasomotor nervous control of the blood vessels in the splanchnic area and lower extemities plays an important part in the adaptation of the circulation to the erect posture. Physiologically, constriction of these vessels is significant in counteracting the fall in arterial pressure which would otherwise arise from the assumption of the erect posture. It is therefore not surprising that extensive sympathectomy often results in pronounced fall in arterial pressure on standing up—orthostatic hypotension—as a result of pooling of blood in the dependent parts of the body This may be so pronounced that in extreme instances the blood pressure falls to unmeasurably low levels when the patient stands erect The drop in pressure affects the systolic more than the diastolic, so that the pulse pressure falls. Orthostatic hypotension is accompanied by reflex acceleration of the heart (orthostatic tachycardia), probably through the carotid sinus. The orthostatic hypotension may be manifested in the erect posture by vertigo, faintness that may go on to syncope, and other cerebral symptoms doubtless due to deficient blood flow through the brain. To prevent these symptoms, it is often necessary for the patients to wear a snug abdominal [illegible]
on the legs. The [illegible]
extent of the sym[illegible]
matic sympathectomy, more pronounced after the thoracolumbar operation, and is said to be usually extreme after total sympathectomy. *Ortho-* [illegible]

[illegible]

much below the preoperative value

Circulation in the Extremities.—The lower extremities are warm and sweating is absent up to a variable level, these are results of lumbar ganglionectomy. The dryness of the skin of the feet and legs may be troublesome. In contrast to the lower extremities, for at least the first weeks or months after operation, the vessels of the upper extremities are constricted with resultant cold hands The consequence is that while normally the skin temperature of the fingers of a patient lying horizontally at room temperature is higher than that of the toes, this is reversed after thoracolumbar sympathectomy. Raynaud-like symptoms may be complained of, but are usually mild and almost always soon disappear. The

blood pressure. This opinion was based on observations with the . . . tration and urea clearance tests. I have not advised operation in patients with significantly impaired renal function. But in cases of this nature which have come under my observation, *there was no evidence that sympathectomy*

ers the Peet[11], ly does occur, but in my experience has been exceptional. Only disappearance of

fertility in the male in any way impaired by the supradiaphragmatic Allen and Adson[1] that lumbar ilation, though in their cases . . . e seen, however, cases in which

libido and potency were unchange cent and improved in 12 per cent male is an absolute desideratum, the lumbar ganglia should be left intact on one side, this does not militate strongly against a worthwhile result from the operation.

Alimentary Tract.—Allen and . . . y be relieved (sympathectomy has bee

. . . should be borne in mind before advising sympathectomy in patients with peptic ulcer

Surgical Complicatior

thoracolumbar sympath collapse, Bechgaard and two stages to two or three months But if the first stage goes smoothly, this seems hardly necessary, to many, the period between operations

Hypertensive Retinopathy.—One of the most remarkable effects of sympathectomy is that on hypertensive retinopathy. Peet early pointed out that the retinal lesions may clear rapidly following the operation. This is very significant for it is very rare for hypertensive retinopathy to disappear spontaneously. Of the 119 patients included in the above tables (page 910), 17 had papilledema, accompanied in 15 by hemorrhages and exudates. After operation, the papilledema, hemorrhages and exudates cleared (sometimes leaving residual atrophy or scarring) in 12 cases. In the 4 instances of longest duration of improvement, the disc and retina were still normal 71, 69, 52 and 45 months after sympathectomy. In 3 patients the retinal lesions recurred after complete clearing. Of the 17 patients in the table with hypertensive retinopathy, 10 were alive at the time of last inquiry. Of the 7 who died, 5 were patients in whom the fundus never cleared, while the remaining 2 succumbed to heart failure without recurrence of the retinal lesions.

Usually, improvement in retinopathy accompanies decrease in blood pressure. However, the retina may clear after operation even though there is no definite fall in blood pressure, or even despite a rise. And when the arterial pressure again rises with time, the retinal lesions do not always recur. In the experience of the writer, contrary to that of Peet and Isberg, the constriction of the retinal arterioles does not disappear after sympathectomy. A working hypothesis of the mechanism by which sympathectomy produces its often dramatic effect on retinopathy is presented above (page 378).

Headache and Other Cerebral Symptoms.—The symptom of essential hypertension most often relieved by sympathectomy is headache. This often occurs in patients in whom rest, sodium restriction and other nonsurgical measures have failed to relieve cephalalgia. Of the 83 patients in the above table (page 910) who suffered from headaches so severe that they were a factor in impelling operation, 64 had no or only slight headache up to the time of the last examination. Among those completely relieved were patients who had suffered from headache for five to fifteen years. Most often completely relieved was a type of headache especially apt to result from hypertension, namely occipital headache frequently radiating down the back of the neck, present when the patient awakens, and often alleviated after he gets up and about. Headache is often improved in patients in whom there is little change in blood pressure.

Other cerebral symptoms, notably restlessness, pounding in the head, tinnitus, inability to concentrate and vertigo are also relieved in a high proportion of the sufferers. The convulsions of hypertensive encephalopathy did not recur in any of the 4 patients of the above series who had them.

The relief of headache and other cerebral symptoms by sympathectomy, which may even occur with li [illegible] explained by diversion of part [illegible] the undenervated portions of the [illegible] has to be reconciled with the finding of Shenkin[37] and his associates, who found with Kety's nitrous oxide method that cerebral blood flow is unaltered following sympathectomy, which would indicate that cerebrovascular resistance falls *pari passu* with decrease in blood pressure.

The symptom which most often plays a primary rôle in deciding on sympathectomy is severe, intractable headache which has failed to respond to nonsurgical treatment. It was seen above that headache is the symptom which most often is relieved by sympathectomy. Other cerebral symptoms, notably restlessness, pounding in the head, inability to concentrate and vertigo may also be weigh[illegible] of sympathectomy; they often disappear after the operation. [illegible] symptoms are not psycl[illegible] favor of operation. Cereb[illegible] (but not cerebral thrombosis) may also incline one toward operation if there are not evidences of widespread arteriosclerotic disease of the brain.

3 *Hypertensive Retinopathy* —The ominous prognostic significance of hypertensive retinopathy has been discussed (page 845). Moreover, hypertensive retinopathy, as the term implies, is a manifestation directly correlated with high blood pressure. It was seen above that hypertensive retinopathy often disappears after sympathectomy. *For these reasons*, unless the patient responds to nonsurgical treatment or one of the con[illegible] sympathectomy is indicated in

[illegible] just mentioned are, in my opinion, almost the only symptomatic indications favoring [illegible] As mentioned above, it does not seem to me that the

[illegible]

ance, the operation would not seem to be indicated unless there is high [illegible] accompanied by symptoms I have not advised opera-

[illegible]

tolic tension, the symptoms of such patients, to such extent as they are not psychogenic, are due to arteriosclerosis Nor does sympathectomy seem advisable in that stage of essential hypertension in which the elevation of blood pressure is only intermittent, such patients usually have a good prognosis for years and the heart and arteries are subject to the strain of elevated pressure only part of the time

Contraindications to Sympathectomy.—1 *Advanced Age* —The older a patient the more apt are his symptoms to be due predominantly to arterio-

[illegible]

sympathectomy and their postoperative troubles have often been severe and protracted For these reasons I believe that sympathectomy is rarely indicated after the age of fifty, and then only for insufferable headache or retinopathy I have not advised the operation in any one over fifty-five years It should be added, however, that this opinion is not shared by others of large experience (*e g*, Hinton and Lord[22]), who have observed [illegible] results in some patients past fifty years

represents a severe psychological trauma. Peet had an operative mortality 579 cases and : dorsolumbar sympathectomy. Both these series included many patients in the malignant phase. In th y was 3.5 per cent. At present, ian 2 per cent if the indications a followed.

Especially during the second stage or soon after, abrupt fall in blood pressure to dangerously low levels with shock may occur. This should be prevented or treated by an intravenous drip of norepinephrine. Injury to the pleura with pneumothorax and hydrothorax is not rare. The latter was present in 23 per cent of Bechgaard and Hammarstroem's patients. The hydrothorax is rarely a source of much trouble. Hemothorax occasionally occurs and very rarely empyema; in 1 patient, the latter took months to clear up.

Widely radiating pains in the segments of the incision are very common. Precisely how they are produced by the operation is not clear. They are often severe and may be agonizing so that opiates or nerve block are required. Usually tl some patients they are still troublesome a

Indications for Sympathectomy.—1 *Failure of Medical Treatment.*—Sympathectomy should not be advised unless the patient has first been given an adequate trial on the nonsurgical measures of suitable rest, reassurance and other psychological guidance, sodium restriction, sedation and the anti-hypertensive drugs discussed above. Only when it has been demonstrated that an intolerable clinical condition is persisting or developing despite such medical treatment does sympathectomy come into consideration.

2. *The Presence of Severe Symptoms.*—Sympathectomy is indicated only in the presence of symptoms directly correlated with elevated blood pressure In my opinion the operation is not called for in the absence of symptoms, no matter how high the blood pressure. This is a change from the view I formerly held that a very high diastolic pressure in youthful subjects indicates sympathectomy even in the absence of symptoms, but the results obtained in such cases have convinced me that operation is not worthwhile. In the earlier days of sympathectomy, I observed several asymptomatic patients in whom the operation was performed purely in the hope of lowering the blood pressure even though they felt entirely well. Although these were clinically early cases in young subjects, one only sixteen years, the blood pressure was not always lowered and almost always rose again within a year or two. I do not believe enough help is to be anticipated from the operation in asymptomatic individuals to justify the slight risk, great discomfort and economic burden entailed It should be borne in mind that individuals with established essential hypertension who are asymptomatic often have a number of years, not rarely ten, twenty or more, of continued freedom from symptoms. Asymptomatic cases with hypertensive retinopathy constitute the exception in which, if they do not respond to medical measures, operation is indicated.

In patients with hypertension *and an* anginal syndrome, Smithwick performs a sympathectomy from the inferior cervical to the twelfth thoracic ganglion inclusive This eliminates the sympathetic innervation of the coronary arteries and heart and averts postoperative tachycardia accompanying orthostatic hypotension. I have not had experience with this type of operation in patients with hypertension and coronary disease.

5. *Congestive Heart Failure* —I have regarded congestive heart failure which has *not been eliminated* by treatment as a contraindication to sympathectomy. Others have observed improvement in congestive failure in hypertensive patients following sympathectomy (page 913).

... manifestation of left ventricular failure, may

6 *Arrhythmias.*—The presence of ... heart block in a hypertensive patient generally indicates a high degree of ... and I have not advised sympathectomy under ...

... hectomy in peptic

Tests for Prediction of Results of Sympathectomy.—Because of the ...

sympathectomy is most likely to be successful in those cases of ... hypertension in which measures that diminish sympathetic tone produce a marked lowering of the pressure or in which the blood pressure shows ...

or nearly normal during the following four test procedures:

1 Administration of $\frac{1}{2}$ grain of sodium nitrite at thirty-minute intervals for 6 doses.

2 Administration of 3 grains of sodium amytal each hour for three successive hours

3 Slow and intermittent intravenous injection of a 5 *per cent solution* of pentothal until there is no further drop in the blood pressure; ordinarily, 0 5 to 1 grain is injected.

4 Hourly determination of the blood pressure during rest and sleep for twenty-four consecutive hours

According to Craig,[11] "If the blood pressure diminishes to normal or nearly normal as a *result of all these* measures, the patient may be considered as a satisfactory candidate for operation. If the *response* of the blood pressure to these measures is inadequate, *the effect* of the operation is almost certain to be unsatisfactory. But even with a satisfactory response to these tests, the operation may be a failure."

2. *Impairment of Renal Function.*—Pronounced impairment of renal function contraindicates operation. This statement contradicts the experience of Peet and his associates, who reported improvement in renal function following sympathectomy. I have not seen increase in the functional capacity of the kidney definitely attributable to sympathectomy. Nor has worthwhile improvement of the blood pressure or symptoms resulted from sympathectomy in the presence of renal insufficiency; some such patients operated when the procedure was first introduced definitely were harmed by the operation. Sympathectomy should not be advised when there is azotemia (NPN above 40 mg. per cent in the absence of heart failure) or the patient is unable to concentrate the urine above a specific gravity of 1.018. Proteinuria of modest degree does not *per se* contraindicate sympathectomy, but massive proteinuria in essential hypertension, in the absence of heart failure, does bespeak considerable renal damage and a worthwhile result from sympathectomy is hardly to be hoped for in its presence

3. *Cerebral Arteriosclerosis.*—Operation should not be advised if there is evidence of widespread, high grade cerebral arteriosclerosis in the form of repeated cerebral vascular accidents, mental deterioration or depression Two patients who had been depressed prior to sympathectomy had to be transferred shortly after operation to institutions with facilities for mental cases requiring restraint. However, a single cerebral hemorrhage from which the patient has made a good recovery is not necessarily a contraindication to operation and indeed, if evidence of cerebral vascular disease other than the focal lesion is absent, may favor the decision to operate. Among over 1,000 operated hypertensive patients who had previously sustained a cerebrovascular accident reported by Peet and Isberg,[6] there were 14 in whom the blood pressure was normal five to eleven years after supradiaphragmatic sympathectomy. About one-third of their patients who were operated after having had a cerebrovascular accident had recurrence of such accidents subsequent to the operation; they do not believe that adequate data are available to establish whether or not operation has beneficially altered the course of the disease in such patients.

4. *Coronary Insufficiency.*—The innumerable clinical variants of the anginal syndrome which usually bespeak high-grade arteriosclerotic narrowing of the coronary arteries with insufficiency have been regarded by the writer as a contraindication to operation. Many hypertensive patients, however, have dull precordial ache often of hours' duration without relation to exercise or emotion which does not necessarily connote coronary narrowing, and this does not necessarily weigh against the advisability of operation. The reasons for the exclusion of individuals with coronary insufficiency were the sudden death of one such patient two days after operation and the *a priori* probability that sudden fall in blood pressure may precipitate coronary insufficiency when the coronary arteries are much narrowed. That rapid fall in blood pressure in hypertensives with coronary arteriosclerosis may engender dangerous or even fatal coronary insufficiency has recently been forcefully demonstrated in patients treated with hexamethonium. That others have observed improvement in angina following sympathectomy for hypertension was mentioned above (page 913).

sclerosis in the heart, brain and kidneys, in the pathogenesis of which hypertension is only a secondary and aggravating factor.

4 In arriving at a rational and not an emotional decision whether or not sympathectomy is advisable in a hypertensive patient, analysis of the symptomatology into the part due to high blood pressure and the part

are due to coincident psychoneurosis

6. Sympathectomy is not indicated in an individual with essential hypertension merely because he is *youthful*, even in a patient in his 'teens known to have high blood pressure for only a short time, the operation may be ineffective

... rarely advisable after the age of fifty

type have a high degree of large vessel arteriosclerosis The operation comes into consideration only if the diastolic *pressure exceeds* 110 mm. Hg in a high proportion of the readings

9 Sympathectomy should not be carried out unless previous nonsurgical treatment with rest, low sodium diet, sedation and *anti-hypertensive* drugs has not produced satisfactory results

11. In the opinion of the writer, sympathectomy is not advisable in the presence of a high degree of coronary or cerebral arteriosclerosis Nor do I advise sympathectomy if there is congestive heart failure unless the latter is quite completely controlled by nonsurgical treatment That others differ with these contraindications was mentioned above.

12 Sympathectomy is indicated in patients with essential hypertension who present none of the above contraindications, who have not responded satisfactorily to nonsurgical treatment, and in whom the disease is becoming aggravated and severe symptoms are present My chief indications have been high diastolic pressure with severe headache or hypertensive retinopathy not responding to protracted medical treatment Patients with hypertensive retinopathy who do not respond to nonsurgical treatment within two months (or less, if vision is being impaired) should undergo sympathectomy even though there are no other symptoms Likewise, if an individual with high diastolic pressure has had a cerebral hemorrhage and recovered well, and there are no other signs of brain damage, sympathectomy is indicated in the absence of response to nonsurgical treatment.

Using these criteria, the writer[39] found in 1948 that sympathectomy had been recommended in about 4 per cent of the patients with essential hypertension whom he had seen in the previous year (by no means all followed the advice) Now, with the present vogue of anti-hypertensive drugs, the operation is advised in an even smaller proportion of cases. Sympathectomy thus helps to fill only a small gap in the great therapeutic problem

Since then, various other tests have been introduced in the hope that they would indicate whether or not sympathectomy would be of help. Lyons[44] and his associates found that all 27 patients whose pressure was still decreased one year after supradiaphragmatic sympathectomy responded to the intravenous injection of 500 mg. of tetraethylammonium chloride before the operation with a fall in pressure greater than 14 per cent of the initial level; 10 of the 31 in whom operation failed had less than a 10 per cent fall in pressure. Grimson[45] et al. found that the effects of Priscol on the blood pressure do not aid in predicting the results of sympathectomy. Russek[46] et al. observed that sympathectomy was effective when continuous caudal anesthesia (1.5 per cent metycaine, upper level of anesthesia fifth or sixth thoracic segment) reduced the blood pressure to normal, while when caudal anesthesia had little effect on the blood pressure the same was true of the operation. However, they state that the test gives information only about the immediate postoperative course and not about what the blood pressure will be a year or more after operation. Using a microplethysmograph, Megibow[47] and his associates found that sympathectomy is generally effective when nitroglycerin produces a pronounced increase in volume pulse amplitude in the fingers and toes; by this method, they predicted the results of the operation in 27 of 30 patients.

The writer's experience has been largely with the sodium amytal test (which is the most widely used) and the hourly determination of the blood pressure, and to a lesser extent with TEAC and other autonomic blocking agents. In a large series of cases, there is some rough statistical correlation between the outcome of these tests and of the operation. But there are so many exceptions that the tests can hardly be regarded as more than a secondary aid to the clinical criteria described above in the decision whether or not sympathectomy is advisable in an individual patient—and individuals are all that the physician deals with. There are many who respond well to the tests (e. g., a fall to normal blood pressure following sodium amytal) in whom the operation proves valueless. Less often, a patient who is obviously unsuited for operation (such as one with azotemia) exhibits a pronounced fall in blood pressure as a result of sedation

Rôle of Sympathectomy in the Treatment of Essential Hypertension.—The present status of extensive sympathectomy may be summarized as follows:

1. Sympathectomy is a palliative and not a curative measure

2. Sympathectomy combats *only* high blood pressure and the symptoms which result directly from it—certain headaches, the liability to (not the consequences of) cerebral hemorrhage, hypertensive encephalopathy, hypertensive retinopathy, and the manifestations of left ventricular strain insofar as they are not due to coronary arteriosclerosis. While renal arteriolar necrosis is a consequence or correlative of high blood pressure, the disease process is then beyond the stage at which sympathectomy can have effect.

3. Sympathectomy does *not* alleviate arteriosclerosis and its consequences, and may indeed aggravate the latter. This is enormously important, for a majority of the serious symptoms of patients with essential hypertension are due not to the high blood pressure *per se* but to the arterio-



was first carried out by Green[..] and his associates ... and severe malignant hypertension (blood pressure up to 270/140 mm.) and severe diabetes. The entire left and at least 95 *per cent* of the right adrenal (a few fragments were left adherent to the vena cava because of bleeding) were removed. The patient was maintained on aqueous and lipidal cortical e... ...costerone *acetate*. Fifteen months later, both

The reader is referred to their publications for details ... intimate experience with the operation has been negligible. The paper of Thorn and his associates gives data on 15 *hypertensive patients in whom* ... adrenalectomy was performed. The observations of Wol-... 10 per cent

ferth's patients with subtotal adre... lumbar sympathectomy was add... alone were not considered adequa... two stages. Thorn's patients were prepared with cortisone and given

patients are maintained on cortisone by injection or mouth; 25 to 50 mg. daily usually suffices The dose must be increased during infection or other stress.

As would be anticipated, bilateral adrenalectomy severely impairs renal conservation of sodium and chloride. Resulting hypovolemia and cir-

salt depletion Even a slight infection or other stress, or brief omission of cortisone, represents the same threat to the adrenalectomized patient as to the Addisonian, and he must be warned of their dangers.

The findings of Thorn and his associates indicate that "depletion of body sodium and chloride content appeared to be a prerequisite for a substantial lowering of the blood pressure" However, in some cases they also observed considerable loss of sodium with little change in blood pressure. The exact nature of the interrelationship between the effects of adrenalectomy on the electrolyte economy and the changes in blood pressure remain to be elucidated

These observations have shown that it is possible to perform bilateral total adrenalectomy on severely ill hypertensive patients and maintain

of essential hypertension. But essential hypertension is so common a disease (or diseases) that even the small proportion of cases in which

results surpassing those attainable by any other method available at present and which are very much worthwhile.

It is not merely a matter of the sympathectomy not being extensive enough, for almost total sympathectomy may fail. Nor is the defect too late operation, for even surgery in clinically early cases in youthful subjects without demonstrable arteriosclerosis may not lower the blood pressure. And although the thoracolumbar operation has notably increased the proportion of worthwhile results, some brilliant successes were obtained with the earlier, less extensive techniques. These facts accord with the conception that multiple entities are included in the concept of essential hypertension, which we are unable to differentiate, and that sympathectomy is of value in only some of them.

ADRENALECTOMY

In the light of the hypotension of Addison's disease and the many hypotheses incriminating the adrenal cortex and medulla in the pathogenesis of essential hypertension, it is not surprising that attempts have been made to treat this disease by ablation of varying portions of the adrenals. As far back as 1914, Crile[48] combined unilateral adrenalectomy with ligation of the thyroid arteries and cervical sympathectomy in an operation for hypertensive disease. While the blood pressure was temporarily reduced, the patient subsequently died after three cerebral hemorrhages. This seems to have been the first attempt at any surgical treatment of essential hypertension; as in other fields, Crile was a pioneer. He later carried out many unilateral adrenalectomies and bilateral adrenal denervations, both alone and in combination with celiac ganglionectomy and division of the major and minor splanchnic nerves, for hypertensive diseases. DeCourcy[49] removed up to three-fourths of each adrenal in patients with essential hypertension. Allen and Adson added partial adrenalectomy to subdiaphragmatic sympathectomy, but later abandoned the adrenal ablation as not improving the results. Neuhof[50] has combined bilateral partial adrenalectomy with thoracolumb
operations, it is difficult to assess how m
actually helps. In several patients whom I
that the addition of adrenalectomy had improved the result of the sympathectomy.

With availability of adrenal cortical hormones, it became feasible to try the effect of total or almost total adrenalectomy in hypertensive diseases. Apart from the considerations mentioned in the preceding paragraph, such attempts were stimulated by Goldblatt's finding (page 320) that adrenal-

The clinical results of renal denervation in hypertensive diseases have not been impressive. Rieder[56] performed unilateral denervation in a patient with nephritis and another with essential hypertension; in both the blood pressure fell markedly and there was subjective improvement for the period of observation of nine months. Chabanier[57] *et al.* carried out decapsulation and denervation of the kidneys in both nephritic and essential hypertension; they observed a pronounced fall in pressure and improvement in subjective symptoms, but the period of observation was of the order of only six months, and the authors themselves anticipated no more than

diseases are those of Page and Heuer,[52] to whose papers the reader is referred for the technique of the operation. In 1 patient with severe essential hypertension, Page and Heuer found that bilateral denervation

After Goldblatt's experiments resuscitated the theory that essential hypertension is secondary to renal arteriolar sclerosis, several attempts were made to treat essential hypertension by surgically inducing collateral circulation to the kidney In experimental renal hypertension due to constriction of the renal artery, the blood pressure can be lowered by producing a collateral circulation between the omentum, spleen or another organ and the kidneys with a narrowed renal artery (Mansfield[60] *et al.*, Cerqua and Samaan[61]) Abrami[62] and his associates first published attempts to do the same in human disease. They carried out nephro-omentopexy in 2 hypertensives by suturing the omentum to the decapsulated kidney, but the outcome was not successful While more favorable results were obtained with this operation by Ritter,[63] similar procedures by de Takats and Scupham[64] and Bruger and Carter[65] also failed to establish the value of the operation

There is no evidence that either renal denervation or induction of collateral circulation to the kidney helps the hypertensive patients, and the operations seem to have been abandoned

PSYCHOSURGERY

As a corollary of psychosomatic theories of essential hypertension

In some of these cases, lowering of blood pressure and symptomatic improvement are described But the data available are too meager to evaluate the effects of leukotomy on essential hypertension. That lobotomy is indicated in hypertensive patients where it would not be called for in the absence of high blood pressure remains to be demonstrated

them on substitution therapy in condition sometimes good enough to work for periods already known to exceed two years. But in the severely ill hypertensives in whom alone the operation comes into consideration, there is an operative and a postoperative mortality. Among Thorn's 15 such cases, there was 1 death on the second day, 2 on the twelfth day and 2 a month after operation. Among Wolferth's 54 patients submitted to subtotal adrenalectomy, there were 2 operative deaths. The experience of these investigators has indicated that the risk is greater and the results poor in patients with severe impairment of renal function. It would appear therefore that the operation should not be done in patients with azotemia.

In only some of the patients has it been possible to maintain significant lowering of blood pressure and yet avert intolerable symptoms of adrenal insufficiency. In others, there has been symptomatic improvement even with little change in blood pressure. The symptomatic improvement may include recession of retinopathy. The outstanding beneficial effect, however, seems to have been improvement in previously intractable heart failure with decrease in the size of the heart and disappearance of edema and other evidences of congestive failure. This improvement is doubtless closely correlated with renal loss of sodium

In many cases, the blood pressure is not

the blood pressure was still 210/120 mm one year after operation. The fact that essential hypertension may persist despite bilateral adrenalectomy speaks strongly against a primary adreno-cortical pathogenesis of the disease.

It does not appear that the place of adrenalectomy in hypertensive disease has been established. But especially in cases with intractable heart failure, further investigative trial of the operation in otherwise hopeless cases would seem desirable.

OPERATIONS ON THE KIDNEY

On the basis of the widely held opinion that there is a pathogenetic relationship between impairment of renal blood flow and hypertension, there have been repeated attempts to alleviate both nephritic and essential hypertension by surgical procedures purported to increase renal blood flow. These have been of two sorts: denervation of the kidneys and attempts to induce a collateral circulation to the kidneys.

Attempts to augment renal blood flow by denervation lack a substantial physiological basis. Rhoads[54] *et al.* found in the dog that section or procaine infiltration of the renal nerves does not affect the blood flow through the kidney. Smith[55] and his associates showed that in normal, nonoperated

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Chapter

31

HYPERTENSION IN THE CUSHING SYNDROME AND PHEOCHROMOCYTOMA

HYPERTENSION IN THE CUSHING SYNDROME

HYPERTENSION is a component of some of the clinical pictures produced by hyperfunction of the adrenal cortex. The association was first pointed out by Edmund Neusser (page 704). In adrenal hyperfunction initiated during intrauterine life and producing pseudohermaphroditism, hypertension apparently does not occur; Drs. S. F. Wilhelm and Meyer Melicow,[1] whose experience has been large in this field, tell me they have encountered no instance. High blood pressure also is rare in those forms of cortical hyperfunction manifested clinically by solely sexual disturbances and generally designed as the adrenogenital syndrome. Contrariwise, hypertension is a cardinal feature of the Cushing syndrome, even when it occurs in the very young (190/130 in the girl studied by Oppenheimer and Fishberg[2] with onset at five and death at twelve years). The cause of the difference in the incidence* of hypertension in the individual forms of cortical hyperfunction is unknown; it presumably is due to variations in the corticoids secreted. Hypertension occurs not only in those instances of the Cushing syndrome which are due to carcinoma or other primary adrenal disease but also in those in which adrenal cortical hyperplasia and hyperfunction are secondary to cortical stimulation resulting from basophilic adenoma or other pituitary disease, thymoma, ovarian tumor, or the changes in the hypothalamus described by Heinbecker (page 732). There is also hypertension in the not insignificant proportion (10 per cent according to Kepler and Locke[3]) of cases of Cushing's syndrome in which definite anatomical abnormalities, apart from the Crooke[4] lesion**, have not been desmonstrable in any of the endocrine glands by the histological techniques used. That hypertension may occur in Cushing's syndrome not of primarily adrenal origin is indi-

* ... of pseudohermaphroditism and 5 of ... cases of Cushing's syndrome studied ...

** Crooke found that whether Cushing's syndrome is due to tumor of the adrenal ... there is replacement of the normal granules ...

cated by its disappearance with the other manifestations of the disease in a patient in whom Dr. S. F. Wilhelm removed a seemingly normal adrenal gland; the patient remained well with normal blood pressure for three years and then died suddenly, apparently of a myocardial infarction.

The hypertension of the Cushing syndrome may be of maximal severity

entered the hospital because of an anginal syndrome. Occasionally, the hypertension and its consequences completely dominate the clinical picture (Case I of Oppenheimer and Fishberg) so that there is no suspicion of a suprarenal tumor until the necropsy. Far more often, however, manifestations other than hypertension predominate in the symptomatology.

Recognition that hypertension is a manifestation of the Cushing syndrome results from demonstration of other features of the latter. Space will not permit detailed description of the symptomatology (*cf.* Soffer[6] and Plotz[7] *et al*), but it includes: Muscular weakness, obesity largely limited to the trunk and face (buffalo type), often with a fat pad over the lower cervical spine and accentuated by contrast with limbs thin

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modest erythrocytosis, a rounded face in which the eyes often appear small and deep set because of puffiness of the cheeks, leading to the appearances described as moon or porcine face, and which may be further disfigured by acne, a thin skin with purplish striae on the abdomen and perhaps the thighs and easy bruising, amenorrhea and very rarely, in contrast to the adrenogenital syndrome, enlargement of the clitoris in the female, loss of libido, impotence and perhaps genital atrophy in the male; frequent emotional and mental disturbances which may culminate in major psychoses (26 per cent of the cases of Plotz *et al*) and suicidal attempts;

ns goes on to severe

in the spine and ribs,

... to spontaneous fractures and is associated with hypercalcuria and rarely metastatic calcification and urolithiasis; increased susceptibility to infections, especially of the skin, which formerly most often caused the fatal termination; in some cases hypochloremic alkalosis, with variable sodium, high bicarbonate, low chloride and low potassium levels in the serum; absolute eosinopenia and relative lymphopenia. Demonstration of an adrenal tumor is exceptionally feasible by palpation, more often it is accomplished by the intravenous pyelogram or perirenal or presacral insufflation. The value of the latter is augmented by the tomogram (Wilhelm).[8] The airograms are not free from error, of 18 cases in which they were considered suspiciously abnormal, only 8 proved to have tumors (Knowlton).[7] Moreover ...

As yet, the theoretically interesting hormonal studies in the urine have not proved of as much diagnostic value as might have been anticipated; while the urinary 17-ketosteroid excretion is high in the adrenogenital syndrome, this is rarely the case in the Cushing syndrome, except for some cases due to adrenal carcinoma, and it may be low. Forbes and Albright[9] found that the excretion of 17-ketosteroids is higher when the adrenals are hyperplastic than when there is an adenoma. In several cases high excretion of 11-oxysteroids has been found. In adrenal carcinomas the estrogen content of the urine is frequently, though not always, high.

Recently, Perkoff[63] *et al.* have shown that the level of 17-hydroxycorticosteroids in the plasma is elevated in Cushing's syndrome and lowered in Addison's disease. Unfortunately, the chromatographic technique is as yet too complex for most hospital laboratories.

If an adrenal tumor is demonstrated in the Cushing syndrome, the *treatment* is surgical. Unfortunately, operation presents much hazard and many patients have been lost soon after the procedure, failing to rally well and succumbing in a shock-like state. Soffer's[6] observations show that the shock is neither hypoglycemic nor identical with an Addisonian crisis, for the electrolytes of the plasma are normal and it is not prevented by cortical extracts and salt solutions; he concludes that it is due to want of some unidentified cortical fraction. The postoperative risk is much greater in the Cushing syndrome than in the uncomplicated adrenogenital syndrome with only sex disturbances, and much greater in those cases of the Cushing syndrome which are due to benign tumors than in those resulting from carcinoma or with bilateral adrenal hyperplasia; apparently, the slowly developing benign tumor leads to functional insufficiency of the other adrenal. The danger seems to have been greatly lessened since ACTH and cortisone have been available. About 100 mg. daily of ACTH intramuscularly should be given for about four days before and after operation in the effort to stimulate the cortical tissue not removed. If appearance of evidences of cortical insufficiency after the operation indicates failure of stimulation by ACTH, cortisone should be given

In cases of the Cushing syndrome not due to adrenal cortical tumor, irradiation of the pituitary and partial adrenalectomy are the treatments most apt to prove beneficial. Irradiation of the pituitary has the plausible basis that the cortical hyperplasia and hyperactivity is due to excessive stimulation by ACTH Transitory and less often protracted improvement have been repeatedly observed (Luft,[10] Johnson[11]). Johnson gives 3 series of 3000 roentgens each, which is more than the dosage usually used With such dosage, in 12 patients with Cushing's syndrome he observed 3 recoveries after long periods of observation, 3 probable recoveries, 4 instances of temporary improvement, and 2 failures.* If irradiation of the pituitary fails, partial adrenalectomy is indicated. Definite and striking remission is produced in some cases by unilateral adrenalectomy (*cf.* Wilhelm and Dickler,[12] case also observed by the writer), to which is usually added

* Arner *et al.* ... rome in 1
patient by elect ... nths after
the operation. ... the theo-
retical interest is great.

partial contralateral adrenalectomy. At the Mayo Clinic, all of one gland and 70 to 90 per cent of the other are removed in two stages (Kepler and Locke). The procedure is not without risk and is by no means always helpful, but it is much the most hopeful treatment at present available. Walters[14] reports a high proportion of excellent results from removal of one adrenal and 90 per cent of the other in 46 patients with Cushing's syndrome. The preoperative administration of cortisone renders rare the postoperative shock that was formerly so great a hazard. Whether total bilateral adrenalectomy [illegible] the treatment of choice in C[illegible] opio-

[illegible]

times testosterone produces transitory [illegible] fundamental course of the disease does not seem to be altered; in my limited experience it has not been worthwhile

HYPERTENSION DUE TO PHEOCHROMOCYTOMA

[illegible] only [illegible] It

The attention of the profession was first called [illegible] of pheochro[illegible] observation of Labbé[15] *et al.* Their patient was a woman, [illegible] although [illegible] tension, [illegible] low as 120/80 mm [illegible] Tremendous fluctuations occurred in the course of the same day During [illegible] presented signs of ex[illegible] the extremities There were symptoms [illegible] cardia, mydriasis, etc The symptoms lasted for many months until they finally terminated in acute pulmonary edema. The sole cause for the hypertension revealed by the necropsy was a pheochromocytoma of the adrenal medulla

Pheochromocytoma producing hypertension is a rare condition. However, since sympathectomies have offered frequent opportunities for exploration of the adrenals and the introduction of pharmacologic tests, more cases have been discovered Smithwick[16] *et al.* discovered pheochromocytoma in 0.5 per cent of sympathectomies for essential hypertension (*cf.* Graham[17]) While most of the cases have been detected between the ages of twenty and fifty, rare instances have been reported in infancy and old age A detailed survey of the literature on pheochromocytoma is included in DeCourcy and DeCourcy's[18] monograph.

cases of pheochromocytoma in the mediastinum and in the neck have been described (Maier,[18] Phillips[19]). The extramedullary tumors are often called paragangliomas. While the tumor is most often single, it may involve both adrenals or be otherwise multiple. MacKeith[20] found 9.7 per cent of the cases bilateral.
ment; it was present in 10
et al., a proportion which is
may produce hypertension, in some of the cases, about one-third according to Kepler and Locke,[22] the growth is large enough to be detected by abdominal palpation. The tumors may be cystic and not rarely exhibit hemorrhages. The large majority are benign and well encapsulated, but a small fraction (9 per cent of the
with infiltrative growth and
characterized by the presence of chromaffine cells, *i. e.*, cells which stain brown after fixation in bichromate, apparently as a result of the reducing action of epinephrine.

The symptomatology of pheochromocytoma is produced by the secretion of epinephrine and norepinephrine—a remarkable experiment *in vivo*. As indicated by the brown staining by bichromate, the tumors contain epinephrine and norepinephrine. The epinephrine content of the tumor may be over 100 times the amount present in a normal adrenal gland—more than 1000 mg. has been found in a pheochromocytoma (*cf.* von Brenner[24] *et al*). The circulation of epinephrine was demonstrated by Beer, King and Prinzmetal[25] in a classical case of paroxysmal hypertension (pheochromocytoma later removed at operation) also seen by the writer. During an attack they showed the "pressor effect of plasma when perfused through the denervated rabbit's ear and the reversal effect of ergotamine." Since then, Lund[26] has demonstrated the circulation of both epinephrine and arterenol in pheochromocytoma Clinically, paroxysms can often be elicited by pharmacologic stimulation of the release of epinephrine or even by mechani-

years, however, it has been shown that the tumors secrete both epinephrine and norepinephrine. In fact, Holton[27] estimates that over half the pressor substance extracted from pheochromocytomas is norepinehprine. The conception has therefore been advanced by Goldenberg[28] *et al.* that differences in the symptomatology of pheochromocytoma result from variations in the amount and proportions of epinephrine and norepinephrine liberated by the individual tumor at the time. They found that when the tumor contains predominantly epinephrine or large quantities of norepinephrine,

hypertension.

* In the case of malignant pheochromocytoma with bone metastases reported by Cross and Pace,[23] removal of the primary growth resulted in disappearance of paroxysmal hypertension.

Clinical Picture.—For a time after La
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growth is not removed.

… stage of paroxysmal hypertension, the anamne-

tumor.

and they may be of iatrogenic origin as a result of diagnostic provocation (see below) For considerable periods the individual attacks may be almost identical. Common manifestations of a full-blown paroxysm are: anxiety, restlessness, tremulousness, *forceful* and usually but not always rapid palpitation, throbbing headache, nausea, vomiting, and constriction in the substernal and epigastric regions. Generalized pallor and coldness of the skin with numbness and tingling of the extremities testify to the vasoconstriction Gooseflesh often appears The veins of the neck are often greatly distended while those of the extremities may be constricted. Profuse sweating usually appears at the attack continues There is generally mydriasis Fever is the rule and may exceed 104° Hyperglycemia is generally present and glycosuria is common. Left ventricular failure with dyspnea, gallop rhythm and pulmonary edema may develop; the latter sometimes proves fatal Cerebral hemorrhage has occurred The attack may last from minutes to over a day. After the attack the patient is usually badly exhausted The paroxysm may terminate in a state of shock

The manifestations of the paroxysm seem to result directly from the liberation into the blood stream of large quantities of epinephrine and norepinephrine Smithwick[18] *et al.* point out that the sweats which appear in the course of an attack are an exception since the sweat glands have a cholinergic innervation. They explain the diaphroresis as an indirect effect of the hyperepinephrinemia resulting from stimulation of parasympathetic centers in the effort to maintain homeostasis, especially of body temperature

In other and probably more numerous instances of pheochromocytoma, the hypertension at the time the patient comes under observation is not paroxysmal and simulates banal essential hypertension so closely that in the past the cases were not

may have been paroxysmal at the onset, this is not evident from the history. The hypertension may attain an extreme degree and may fluctuate much as in essential hypertension. Differences between the elevated blood pressure in essential hypertension and pheochromocytoma brought out by the studies of Smithwick *et al.* include much greater frequency of postural hypotension and a smaller incidence of hyperreaction to the cold pressor test in pheochromocytoma. The hypertension may go on to the malignant phase with hypertensive retinopathy, necrosis of the renal arterioles and renal insufficiency.

Most of the patients exhibit hypermetabolism; the basal metabolic rate may exceed plus 50 per cent. This is often accompanied by loss of weight, tachycardia and an anxious expression of the face. Sweating and tremulousness are often prominent features. In these cases there may be confusion with Graves' disease (McCullogh and Engel[31]) or psychoneurosis Hyperglycemia, a diabetic sugar tolerance test and glycosuria are common, and cases have been regarded as diabetic (DeVries[32] *et al.*). With removal of the tumor, the diabetes vanishes (Duncan[23] *et al.*). Hyperglycemia is absent in some of the cases, especially in children, which has been attributed to relatively low glycogen stores in the liver in the very young (Cahill and Aranow[34]) There may be remarkable insensitivity to epinephrine; Maycock and Rose[35] had to exceed a subcutaneous dose of 1.5 cc. of a 1:1000 solution before there was any effect.

The course may be protracted over years and, as in essential hypertension, cardiac, cerebral or renal manifestations may be prominent. In 51 cases reviewed by Green, enlargement of the heart was present in 17, abnormal electrocardiograms 10, myocardial infarction 1, hemiplegia 2, proteinuria 20, and azotemia 2; "nephrosclerosis" was found at necropsy in 7 of 16 patients. The remarkable fact that some degree of hypertension often persists for a considerable time after removal of the tumor (Goldenberg[28] *et al.*) is perhaps an expression of the frequency of damage to the renal vessels by the hypertension. Sudden death may occur after minor trauma or operation (Cahill and Melicow[1]); the diagnosis may not have been previously suspected.

Diagnosis.—In patients with paroxysmal hypertension the clinical features mentioned may lead to strong suspicion of the diagnosis. However, it should be borne in mind that some patients with essential hypertension exhibit fluctuations in blood pressure simulating those of pheochromocytoma The resemblance to pheochromocytoma may be increased when the rise in pressure is accompanied by such manifestations of emotional and autonomic lability as crying, tremulousness, tachycardia and sweating. Such patients are often suspected of pheochromocytoma and have been fruitlessly explored. In young children, a remarkable group of cases of paroxysmal hypertension simulating pheochromocytoma have recently been described by Riley[36] and Aronson[37] and their coworkers. The attacks were characterized by diastolic hypertension (exceeding 120 mm in a four-ye
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as manifestations of an excessively labile autonomic nervous system.

When pheochromocytoma produces continuous hypertension, the clinical features are most often not strongly suggestive of the existence of the tumor. Actually, most instances of continuous hypertension which ultimately prove to be due to pheochromocytoma have been regarded for considerable periods, or until sympathectomy or necropsy, as essential hypertension. The cold pressor reaction (page 764) seems to be less often excessive in hyper- (Smith- of much ... On rare occasions, suspicion that a hypertensive subject may have a pheochromocytoma is aroused by palpation of an abdominal tumor or demonstration of downward displacement of the kidney in the intravenous pyelogram Palpation of the tumor may precipitate an attack. It should be remembered that the tumor itself may not be palpable but may displace a kidney or the liver so that these viscera become palpable. In a patient with hypertension of over five years' duration the liver became palpable Peritoneoscopic examination at another hospital showed what seemed to be a normal, presumably ptosed, liver. At necropsy a huge pheochromocytoma displacing the liver was found, the tumor was benign and could readily have been removed Demonstration of a tumor may be effected by perirenal insufflation with oxygen, especially if supplemented by laminography (Wilhelm[8]) Perirenal insufflation by the pre-sacral route promises to be particularly helpful. Kepler and Locke[14] regard perirenal insufflation as contraindicated, presumably ... danger of ... at I have ... t danger; ...

Pharmacologic Tests.—In recent years the diagnosis of pheochromocytoma has been greatly furthered by the introduction of two varieties of pharmacologic test In the one an adrenolytic ... dministered to a ... ure if the hyper-

... of these catechols. Piperoxane has close structural relationships to the sympathomimetic amines ... be that the adrenolytic ...

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unknown. False positive *benzodioxan* tests were also early reported in the absence of uremia by Taliaferro[48] *et al.* and Weiss and Neibrief,[49] but the absence of pheochromocytoma was not proved by *necropsy*. Since then, ... have published a case of hypertension

... for circumspection in the interpretation of the effects of ... d similar substances. *A number* of fruitless explorations have been carried out because of falsely positive pharmacologic tests.

Other adrenolytic compounds that have been used to test for pheochromocytoma are *dibenamine* ... related to Priscoline). Spear an ...

... introduced by Longino[52] and his associates. Emlet *et al.* recommend a standard dose of 5 mg. because 10 mg. often depresses the blood pressure in patients with hypertension not due to pheochromocytoma. They state that regitine produces fewer side reactions than piperoxane and also that the reduction in blood pressure is more prolonged. Gifford[54] and his associates used *regitine as a test in 259 patients, 7 of whom had* pheochromocytoma. They found that when given intravenously in doses of 5 mg. regitine produces a marked fall in blood pressure in hypertension due to *pheochromocytoma.* *While they also observed some depressor effect in* two-thirds of their patients with essential hypertension, this was usually less than 35/25 mm. Regitine has the advantage over piperoxane that it is given by simple injection and an intravenous infusion need not be set up. Moreover, the hypotensive effect lasts longer and reactions are not as severe as those which sometimes follow piperoxane. Regitine may be given intravenously or intramuscularly. Following intravenous injection the depressor effect appears within two or three minutes and lasts from a few up to about *fifteen minutes* ...
which I have no experience, ...
twenty minutes and lasts abo ...
tests have been observed under conditions similar to those in which misleading reactions occur with piperoxane.

It would appear that none of the tests for pheochromocytoma with adrenolytic substances give absolutely unequivocal results. In doubtful cases more than one test should be used. For routine screening of hypertensives to detect pheochromocytoma, Regitine is perhaps *preferable* because of greater ease of administration and less pronounced side reactions. It has been found that sedatives given within twenty-four hours before either the piperoxane or Regitine tests *favors* the occurrence of false positives.

intravenous drip of physiological saline is started through a *three-way stopcock*. The blood pressure is repeatedly measured on the other arm. After it has become stabilized, the piperoxane is injected over a two-minute *period in 0.2 per cent solution* from a syringe through the three-way stopcock; this averts perturbations in blood pressure due to *venipuncture* (piperoxane hydrochloride is available in ampoules containing 10 cc. of 0.2 per cent solution). The blood pressure is then recorded at *one-minute intervals* until it returns to pre-injection levels.

In the presence of hypertension due to circulating *epinephrine or arterenol*, piperoxane produces a fall in blood pressure initiated in from seconds to four minutes and which may last as long as *fifteen minutes*. The maximum fall in systolic and diastolic pressures may exceed 50 mm., but *in most tests* it is less. In normal persons and in essential hypertension there is usually *a slight pressor effect, in the latter group, the rise in pressure* may be marked.

In normotensive individuals and those with hypertension due to *pheochromocytoma*, the side-effects of piperoxane are usually slight and transitory, they may include palpitation, tremulousness, slight headache and *vertigo*. But in patients with essential hypertension the side-effects are often much more pronounced and distressing; there may be marked rise in pressure with severe headache. On rare occasions, hypertensive encephalopathy with violent headache and convulsions has been observed (Drill,[40] Green and Peterson[41]). In 1 patient with essential hypertension, injection of piperoxane was followed by extremely severe headache with stiffness of the neck and disorientation; the patient's condition was alarming for over two hours. Since this case, the writer has not used the piperoxane test unless there was actual suspicion of pheochromocytoma.

Both false negative and false positive reactions to piperoxane have been observed. Goldenberg and Aranow[42] cite 3 cases of persistent hypertension reported by different observers and proved to be due to pheochromocytoma in which the piperoxane test was negative. Others have since been reported by Conley and Junkerman,[43] Mason,[44] and Koonce[45] *et al.*, in the case of Koonce piperoxane produced a marked rise in blood pressure. Goldenberg and Aranow observed that hypertension persisted for a significant time after removal of the tumor in 7 of 12 patients with pheochromocytoma. On the basis of this and other evidence, they believe that after epinephrine secretion has initiated hypertension, secondary mechanisms may participate

by Calkins[46] *et al.* was indicated by an immediate fall in blood pressure on ligation of the tumor pedicle, they suggest that in such cases the benzodioxan injected may not be enough to compete successfully with the amount of epinephrine present. False positive reactions to benzodioxan often occur in uremia (Goldenberg,[47] Emlet[48] *et al.*) The latter observed a significant fall in blood pressure from piperoxane in 5 of 11 patients with hypertension and uremia, the positive tests occurring in those with very high nonprotein nitrogen. The mechanism of the positive benzodioxan test in uremia is

. . . a pheochromocytoma was first ac-

. . . tests are . . .
clinical picture . . .
chromocytoma . . .
tumors, especially . . .
be anterior.

The operation presents redoubtable hazards, and a number of patients have been lost during or immediately after the procedure. Cahill and Aranow give the operative risk as less than 16 per cent. At any time from the initiation of preoperative preparation, but especially while handling the tumor, there may be sudden extreme rise in blood pressure as a result of release of epinephrine and norepinephrine. Following the operation . . . reduced to about

release of large quantities of catechols during the procedure . . . may be made to prevent the effects of epinephrine discharge during the operation by the administration of dibenamine (page 937) or piperoxane (20 mg. intravenously, perhaps repeated in half an hour). The shorter-acting piperoxane is perhaps preferable, for Decker[33] et al. point out that if

5 to 10 mg. Following the operation, an intravenous drip of norepinephrine (4 mg. per liter) may avert dangerous hypotension (Swan,[35] Cahill and Monteith[34]) and seems to have fewer side-effects than epinephrine. The norepinephrine may be needed for twenty-four hours or more. Cortical

the removal of the only pheochromocytoma, persistence of the hypertension should cause one, especially in children, to consider the possibility of a second tumor

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Knowlton Bull.

Histamine and Other Stimulants of Epinephrine Secretion.—In patients with paroxysmal hypertension (and in those with low-grade continuous hypertension), evidence of pheochromocytoma may be sought by injecting a stimulant of epinephrine and norepinephrine secretion. The stimulant most commonly used is *histamine*. Hyman and Mencher[55] produced attacks by the injection of histamine and the procedure was developed as a test for pheochromocytoma by Roth and Kvale.[56] The latter investigators found that the rapid intravenous injection of 0.025 mg. of histamine base into patients with pheochromocytoma reproduces the spontaneous attacks. In their 3 patients with pheochromocytoma, the injection of histamine produced a rapid rise in blood pressure which reached its peak within two minutes and returned to the control level in five to ten minutes; the rise in pressure was accompanied by the symptoms of a spontaneous attack. Roth and Kvale found that in patients with pheochromocytoma histamine produces a far greater rise in pressure than the cold pressor test, while in all others any rise was less than the cold pressor response. The histamine test should not be used in patients suspected of pheochromocytoma who have considerable hypertension at the time; a dangerous reaction may ensue. Complete reliance should not be placed on the histamine test; Decker[57] *et al* and others have observed pheochromocytomas with negative response to histamine. Calkins[46] and his associates observed a rise in blood pressure after histamine in a hypertensive patient without pheochromocytoma, but Roth[58] found that such a rise occurs four to ten minutes after injection and is due to the headache.

In a patient with pheochromocytoma, LaDue[59] *et al* produced hypertension by the intravenous injection of 400 mg. of *tetraethylammonium bromide*; they suggested that if dangerously high levels were thus produced, they could be controlled by standing up However, Roth and Kvale obtained negative results with tetraethylammonium bromide in some patients with pheochromocytoma and a rise in pressure in some cases without a tumor. Subcutaneous injection of 25 mg. of *mecholyl* was used by Guarneri and Evans[60] in a patient with pheochromocytoma; after an initial fall, the blood pressure rose sharply within two minutes and returned to the control level within fifteen minutes.

Catechol Assays in the Urine.—In 2 cases of pheochromocytoma, Engel and von Euler[61] demonstrated an *increased catechol content of the urine*, the proportions of epinephrine and arterenol were the same in the urines as in the tumors. Lund[26] also found that the urine of patients with pheochromocytoma contains 10 to 100 times as much pressor amines as normal Recently, Goldenberg[62] has carried out extensive studies of the catechol content of the urine. He found that in health the urine contains between 20 and 50 micrograms of catechols in twenty-four hours, of which about 90 per cent is norepinephrine and 10 per cent epinephrine. Goldenberg found the catechol content of the urine in essential hypertension between 75 and 100 micrograms in twenty-four hours. In pheochromocytoma he obtained daily catechol excretions of between 600 and 2700 micrograms in sustained hypertension and up to 580 micrograms during attacks of paroxysmal hypertension. If Goldenberg's procedure can be applied in hospital laboratories, it should enormously facilitate the diagnosis of pheochromocytoma.

Chapter

32

RENAL AND HYPERTENSIVE DISEASE IN PREGNANCY

The occurrence of Bright's disease ("néphrite albumineuse") in pregnant women was observed by Rayer,[1] who already differentiated the renal disorder which appears late in pregnancy from that which was present before conception and becomes manifest early in gestation. He also noted ... type often clears up after the su ... Shortly

Dieckmann's[3] recent monograph.

The primary differentiation among the renal and hypertensive complications of pregnancy, mandatory from both practical and theoretical points of view, is between:

1. *Forms of Bright's disease which may also affect the non-pregnant woman.* They may either have been present before conception or first develop during gestation.

2. The unique renal and hypertensive manifestations which take origin only during pregnancy or immediately post partum and have long been been included in the collective concept of toxemia of pregnancy. In recent years, these disorders are generally designated as either preeclampsia or eclampsia. However, there is nothing basic about this differentiation, which is merely a clinical convenience. It will be seen below that the cerebral symptoms which are the hallmark of eclampsia are manifestations of hypertensive encephalopathy, which may occur in diastolic hypertension of any nature.

PREEXISTENT BRIGHT'S DISEASE AND PREGNANCY

Glomerulonephritis.—In the past, the diagnosis of acute or chronic glomerulonephritis was made too often in pregnant women, many cases of essential hypertension or toxemia of pregnancy were thus labeled. The actual incidence of glomerulonephritis in preganacy is extremely small. Dieckmann found that less than 0.1 per cent of pregnant women have acute or chronic glomerulonephritis or nephrosis; these patients comprised 1 per cent of his toxemic patients. I have seen very few instances of acute

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interrupted early in these

The fetal mortality whe
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infarction of the placenta is very frequent, and renal disease of various
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supplying the placenta begin earlier than normally in renal and vascular disease (Schwarz and McNalley[7]).

Insofar as the effect of pregnancy on the mother with glomerulonephritis is concerned, we have mentioned that it is generally, though by no means always, decidedly adverse. Increase in hypertension and proteinuria, the appearance of edema, retinal changes or nitrogen retention may afford objective evidence of the deleterious effects of pregnancy. Termination of
...

pregnancy, and the downward course may continue until uremia appears. Succeeding pregnancies are more often followed by renewed deterioration of the glomerulonephritis, generally at an earlier period and in a more severe form. On the other hand, there are also cases in which proteinuria of nephritic origin is present and the patient passes through a number of pregnancies without evident harm.

Treatment.—In view of the great risks to the mother and the high fetal mortality, a woman known to suffer from glomerulonephritis should be advised not to become pregnant. But the mere fact that a woman had acute glomerulonephritis in the past, from which she has completely recovered with normal urine and blood pressure, is no contraindication to pregnancy. I have never known a renewed attack of glomerulonephritis in such circumstances, and there is no evidence that such women are especially

... is much the same as
... If there is marked hypertension, renal insufficiency with nitrogen retention, or hypertensive retinopathy, the danger to the mother is great and the uterus should be emptied. Even patients with but slight symptoms should be very carefully watched, any increase in hypertension or edema, or particularly the appearance of retinal changes, calls for prompt termination of pregnancy. Increase in proteinuria is also a danger sign. If the glomerulonephritis is severe or in any way symptomatic, pregnancy should be terminated as soon as feasible, if mild at any indication of intensification. It is always to

glomerulonephritis in pregnancy. It is true that pregnancy is occasionally well borne by women with chronic renal disease, but such instances are decidedly exceptional, much more so than in mitral stenosis. Previously asymptomatic renal disease may first become manifest during pregnancy or is discovered solely as a result of routine examination of the urine in a patient without complaints. In such cases the presence of marked hypertension, hyposthenuria, retinal arteriosclerosis or considerable cardiac enlargement may reveal the process to be of considerable standing. Moderate cardiac enlargement can be detected with assurance only early in pregnancy, for later estimation of the size of the heart is handicapped by the displacement incidental to elevation of the diaphragm.

Further investigation is required regarding the mechanism of the progressive impairment of renal function, rise in blood pressure and exacerbation of other symptoms that so often occur during pregnancy in women with glomerulonephritis. Exacerbation of glomerulonephritis may doubtless result from streptococcic throat infection during pregnancy quite as it does under other circumstances (page 600) But in the large majority of instances there is no evidence of this. Among the factors that may be concerned in aggravating glomerulonephritis during pregnancy are increased excretory work, hormonal alterations favoring hypertension and fluid retention, and pressure on the ureters in the last months—but none of these are more than hypothetical mechanisms unsupported by any evidence. Fahr[4] and others have published cases in which necropsy, in addition to chronic glomerulonephritis, revealed the changes in the kidney and liver which are often found in specific toxemia of pregnancy.

The clinical picture of glomerulonephritis is that which is generally designated as "nephritic toxemia" The most important characteristic, from the diagnostic point of view, is that the manifestations of glomerulonephritis, contrary to those of initial toxemia of pregnancy, are almost invariably present before the twenty-fourth week of pregnancy—usually at the first examination. The most frequent complaints are headache, lassitude, weakness, anorexia, pallor and swelling of the ankles; visual disturbances less often bring the patient to the physician. Examination reveals marked proteinuria, usually red blood cells and casts in the sediment, generally marked arterial hypertension, and often edema of various parts. The number of erythrocytes in the sediment is usually much greater in glomerulonephritis than in toxemia. Hypertensive retinal lesions may be present. Contrary to initial toxemia, study of renal function often reveals marked impairment of concentrating power, in which event there may be nitrogen retention in the blood The presence of significant azotemia is a strong indication that the patient has glomerulonephritis and not initial toxemia.

It is generally believed that glomerulonephritis in a pregnant woman strongly predisposes her to eclampsia gravidarum. On the other hand, in Heynemann's[5] experience eclampsia was extremely rare in women with glomerulonephritis Corwin and Herrick[6] find that in glomerulonephritis convulsions are "infrequent, late and probably uremic in character." This has also been my experience. However, convulsions, amaurosis, coma, etc. do occasionally occur in pregnant women with hypertension due

however, a considerable proportion of women with essential hypertension, which is asymptomatic and with not very high blood pressure (under 180/110 ... sults are perhaps ... and rest. In fact, ... al hypertension of modest degree to fall during ... middle trimester when the bl... havior ... apt this is to occur, ... in the rabbit, and less common in the d... ... On the other hand, experimental hypertension due to administration of desoxycorticosterone acetate and sodium chloride is not affected by pregnancy (Page and Glendenning[10]).

More often, unfortunately, patients with essential hypertension do not

... my experience, the fetal death rate due to *abruptio placentae* or other

... against pregnancy Should a blood pressure of up to about 170/110 mm. be found early in pregnancy without any symptoms, the woman should be warn-

... symptoms appear despite the treatment, pregnancy should be terminated

... it is the experience of the writer that the pregnancy will rarely be carried to a successful termination and that the mother's disease is aggravated. For these reasons, it is my opinion that pregnancy under such conditions should be terminated A dilemma may be posed by cases in which essential hypertension becomes severe or is first found when the period of viability is approaching, in such instances, with the patient greatly desirous of having a baby, it may be the better judgement to attempt to carry along with bed rest and sodium restriction until there is a good chance of getting a viable baby My experience with antipressor drugs in such cases is negligible, but they may prove to be of value. Pregnancy in a patient with essential hypertension in the malignant phase is rare, interruption is almost always called for.

be borne in mind that the change for the worse may occur with fulminating rapidity, so that procrastination in terminating pregnancy may be dangerous. Especially close watch should be kept for hemorrhage due to *abruptio placentae* and for acute left ventricular failure.

Chronic Pyelonephritis.—Acute pyelonephritis is a common complication of pregnancy (page 643). It is not associated with hypertension or edema, does not call for other than antibiotics and local treatment, and rarely interferes with the progress of pregnancy. Contrariwise, just as chronic pyelonephritis may produce hypertension in the nonpregnant state, it is among the causes of the hypertensive syndromes of pregnancy. Peters[5] and his associates found evidence of pyelonephritis in 13 per cent of 320 patients with so-called "toxemia" (using the term toxemia as a collective designation for all the hypertensive and edematous syndromes of pregnancy). They also found that 27 per cent of 93 cases of pyelonephritis during pregnancy developed hypertension, sometimes accompanied by edema, before term. In the writer's experience, the proportion of patients with hypertensive complications of pregnancy in which pyelonephritis played a part has been smaller than this. But among the cases which have been termed "nephritic toxemia" in the past, and have generally been taken as examples of chronic glomerulonephritis, a not inconsiderable fraction were actually due to chronic pyelonephritis.

Essential Hypertension.—A high proportion of the pregnant women in whom elevated blood pressure is found are suffering from essential hypertension. This is especially true of those past thirty years of age. In the experience of the writer, a majority of the women under thirty and a very large majority (probably over ninety per cent) of those over thirty with elevated blood pressure have essential hypertension and not toxemia of pregnancy as characterized below. In most of the cases this is proved immediately by the finding of hypertension at the first examination early in pregnancy or a history of previous hypertension. There are, however, [illegible]

have essential hypertension, or the toxemia is superimposed on essential hypertension. There are many cases first seen late in pregnancy in which one can not be sure whether the patient has specific toxemia or essential hypertension.

When a woman with essential hypertension becomes pregnant, the dangers to both mother and fetus are very considerable. However, they are not nearly as great as they were two or three decades ago. At that time, Corwin and Herrick,[6] based on the extensive experience and ideal condi- [illegible] Hospital wrote that "Very few women who [illegible]

several of the phenomena previously included in the toxemia of pregnancy. Thus, some of the anemias are due to iron deficiency; at least many instances of neuritis to deficiency of vitamin B; early vomiting often to psychoneurotic mechanisms and perhaps in other cases to hormonal disturbances.

The result has been that in recent years the designation toxemia of pregnancy has been reserved for what had always been its stronghold, namely, a group of renal and hypertensive manifestations almost always initiated in the later months of pregnancy and sometimes culminating in eclampsia. The following discussion will be confined to those renal and hypertensive manifestations which are not present at the beginning of pregnancy and generally appear in the last trimester. *Faute de mieux*, they will be designated by the almost universally used term toxemia of pregnancy. But it is to be emphasized that this designation is without rationale and should be discarded as soon as the nature of the phenomena is elucidated, there is no reason to assume that the clinical pictures in question result from the circulation of a "toxin" in the usual immunologic sense.

Statistics of the incidence of toxemia of pregnancy have varied enormously (*cf* Dieckmann[4] for a detailed survey in different parts of the world). To some extent these differences may be real. However, they are certainly not as great as the differences in the incidences of eclampsia, which, especially from the less advanced countries, are what are most often reported, and tacitly assumed to parallel the incidence of toxemia. This is unjustified, for eclampsia can almost always be averted and its incidence is less the better the prenatal care. Thus, there is far more eclampsia among the negro than among the white population in the United States, but that there is a similar difference in the incidence of the underlying toxemia requires further demonstration. Moreover, it is often difficult to decide if a given amount of water retention in pregnancy is to be regarded as abnormal, whether minimal proteinuria is to be regarded as toxemic, and what is the upper limit of normal blood pressure in pregnancy. Statistics from leading maternity hospitals in the United States for the years 1947 to 1950 collated by Dieckmann revealed an incidence of nonconvulsive toxemia of pregnancy of 7.9 per cent with a mortality of 0.14 per cent, and of eclampsia of 0.155 per cent with a mortality of 6.34 per cent. In recent years the incidence of eclampsia and the death rate from toxemia of pregnancy have decreased enormously in the United States and many other countries. In Beth Israel Hospital in the past three years there has been 1 case of eclampsia in about 7500 deliveries. In New York City the decline in incidence of eclampsia and mortality from toxemia has occurred in each of the individual racial strains and is due to better management, that the underlying toxemia has decreased in incidence is not evident. It is rare for toxemia to become manifest before the twenty-fourth week of pregnancy and most of the cases are not definite until the thirtieth week or after. [illegible] predisposing [illegible] toxemia, but it is quite possible that this is effect and not cause. Toxemia may develop very early in the presence of hydatidiform mole. Diabetes is also a predisposing cause.

Considerable series of patients who went through pregnancy after sympathectomy for essential hypertension have been reported by Newell and Smithwick[11] and Peet[12] *et al.* From these reports it appears that in women whose blood pressure has been reduced close to normal by the operation, there is an excellent chance of successful pregnancy. The 14 women reported by Newell and Smithwick had 17 living infants and 1 stillbirth. In none of the cases did the blood pressure rise prior to the seventh month, but in 5, pregnancy was terminated prematurely because of increasing proteinuria and hypertension in the third trimester. Peet *et al.* found that their patients whose blood pressure had been reduced close to normal had uneventful pregnancies, but there only 2 living babies among 10 pregnancies in which blood pressure had remained high after sympathectomy. Peet performed sympathectomy during the second trimester in 5 cases; 2 living babies were born. The writer has not advised sympathectomy during pregnancy.

MANIFESTATIONS INITIATED ONLY DURING PREGNANCY: TOXEMIA OF PREGNANCY

Lever,[2] who first observed that the urine of women with eclampsia gravidarum contains protein, considered the renal damage the result of compression of the renal veins by the enlarged uterus. Frerichs[13] subscribed to this view, but thought that changes in the composition of the blood resulting from pregnancy also played a part. He regarded eclampsia as a form of uremia. The theory that the renal lesions of pregnancy result from compression of the renal veins was overthrown by Bartels,[14] who considered the process in the kidneys to be a "parenchymatous nephritis" akin to that which follows scarlet fever. Shortly thereafter, Leyden[15] showed that the renal lesions found in eclampsia patients are essentially degenerative. He believed that they differ from the changes encountered in any of the forms of Bright's disease occurring in the non-pregnant state and, therefore, coined the term "kidney of pregnancy" (Schwangerschaftsniere) to designate the renal lesions which are specifically correlated with pregnancy.

The Concept of Toxemia of Pregnancy.—Subsequently, the view gained wide currency that what Leyden had called the kidney of pregnancy and eclampsia gravidarum are individual manifestations of so-called toxemia of pregnancy. In its heyday, the concept of the toxemia of pregnancy included such variegated phenomena as hyperemesis in the early months of gestation, the renal manifestations which usually develop in the last trimester, eclampsia, acute yellow atrophy, dermatitis, psychosis, neuritis, anemia, and practically all the other complications of pregnancy which are not blatantly of septic origin or explained by alterations in the genital tract. It was held that these complications are individual manifestations resulting from the circulation of some "toxin." Williams[16] for many years opposed this widely held conception of a single cause for all these pathological complications of pregnancy; he believed that "several distinct entities have to be dealt with and that any attempt to gather them into a single group will retard the eventual discovery of their respective causes." Actually, studies since then have elicited the pathogenesis of

... has been attributed by many investigators to changes
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and Peters describe the ... ening of the walls of the glomerular loops. This thickening of the walls of the loops is sometimes sufficient to impinge markedly on the lumen and ... ally to obliterate it. The result may be a bloodless state of a ...

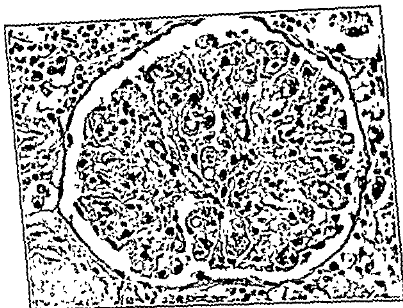


FIG 49 – Glomerulus of a forty-year-old woman who succumbed in the eighth month of pregnancy after five eclamptic convulsions The walls of the loops are markedly thickened

thickening of the basement membrane of the capillaries* and to swelling of the epithelial cells The thickening of the walls of the loops may impart to them a rigid, "wireloop" appearance There may also be fatty changes in the walls of the loops and both the endothelial and epithelial cells may

* While this interpretation has been widely accepted, in recent years doubts have ... actually due ... collagen and ... as thickening ... plasm of the ... likewise found no thickening of the basement membrane by means of what he regards as a specific stain.

PATHOLOGICAL ANATOMY OF TOXEMIA OF PREGNANCY

Most of out information regarding the pathological anatomy of toxemia of pregnancy is derived from individuals who succumbed to eclampsia or left ventricular failure with pulmonary edema. Necropsy may reveal edema of the brain, which is correlated with the final eclampsia, and less often jaundice or widespread hemorrhages. Cerebral hemorrhage also is found in rare cases. But the lesions which have been thought to have possible causal relationship to the toxemia of pregnancy are those in the placenta, liver and kidney.

The Placenta.—There have been many attempts to correlate morphological changes in the placenta with toxemia of pregnancy. Traut and Kuder[17] were unable to establish a definite connection between placental changes and toxemia. However, the observations of Bartholomew[18] and Falkiner[19] show that widespread, predominantly acute infarctions of the placenta are rather characteristic of toxemia. Harer[20] found the degenerative changes in the placenta more marked in toxemia than in others. Histologically, the placenta in toxemia reveals premature aging with syncytial degeneration in excess of the normal (Tenney and Parker[21]). The significance of these changes is not clear, but the observations of Tenney and Parker indicate that they antedate the clinical manifestations of the toxemia.

The Liver.—The classical hepatic lesions of toxemia of pregnancy consist in hemorrhagic necrosis, which seems to be initiated in the periportal areas, but may become very widespread. It is to be emphasized that the hepatic lesions are not constant; a patient may have had severe hypertensive toxemia and yet reveal little change in the liver. Dexter and Weiss[22] observed hepatic lesions in 12 of 25 patients with toxemia. Sheehan[23] found hepatic lesions in nearly all patients who succumbed to eclampsia, but in only about a quarter of those who recovered from eclampsia but died during the puerperium of other causes. Moreover, the appearance of the hepatic necrosis indicates that at least the major changes are of recent inception, even though hypertension, edema and proteinuria had been present for months. It would appear that the hepatic lesions are due to circulatory disturbances, in some instances, at least, extensive thromboses of small branches of the hepatic artery appear to play the predominant role in the causation of the hepatic necrosis, but the possibility that the *primum movens* is intense vasoconstriction in the liver is also to be borne in mind. In any event, it appears that the hepatic lesions develop late in the course of the toxemia, and there is no evidence that they produce the latter.

The Kidneys.—These organs are usually, though not always, somewhat enlarged. The cut section of the cortex appears cloudy and the medulla engorged. The general architecture of the kidney is not disturbed and the changes are first revealed by the microscope.

Hyaline and fatty droplets may be seen in the tubular epithelium, though to a varying degree. Casts are often present. Changes of similar [illegible], and they [illegible] less than [illegible] do not appear [illegible] 17 of the 31 cases of eclampsia and preëclampsia studied by Fahr,[4] though often but sparingly.

THE NATURE OF TOXEMIA OF PREGNANCY

Speculations [illegible] pregnancy have been so numerous a[illegible] theories" Only [illegible] historical exposition the reader is referred to the monograph [illegible]

The Role of the Kidneys.—Because of the prominence of edema and proteinuria, what is now termed toxemia of pregnancy was originally re[illegible] [illegible] the kidneys However, both the clinical [illegible]

[illegible]

nate the edema, though they may contribute secondarily [illegible] proteinemia. That the hypertension of the toxemia of pregnancy is renal in origin has not been proved; it is possible that the widespread vasoconstriction which elevates the blood pressure is also responsible for the renal lesions.

Pressure on the Ureters and Renal Veins.—It has often been thought (*cf.* Paramore[19]) that the pressure of the enlarged uterus on the ureters and/or renal veins may be concerned in the pathogenesis of toxemia of pregnancy [illegible] [illegible]ography shows that in the later months of pregnancy [illegible] degree of [illegible] Toward the end of pregnancy [illegible] the venous return from the kidneys. Both these mechanisms tend to impede renal blood flow and when Goldblatt produced hypertension by constricting the renal artery, the theory that pressure on the ureters might [illegible]

[illegible]

the enlarged uterus plays a part in the pathogenesis of toxemia of pregnancy seems an unsupported theory.

The Role of the Liver.—Hepatic lesions are often found in toxemia of pregnancy and may contribute to the symptomatology. However, these lesions are not the fundamental cause of the disease, for they are often absent Moreover, perhaps the most important single manifestation of

be swollen. According to Fahr, the number of nuclei in the involved glomeruli is not increased; indeed, he finds the density of nuclei markedly decreased in the cases with severe changes. On the other hand, Bell states that while there is usually only a slight increase in the number of endothelial nuclei in the glomeruli, in exceptional instances there is such marked proliferation of these cells that they become the chief factor in obstructing the capillary lumen. In 2 instances of eclampsia that I examined, there seemed to be no definite change in the number of nuclei within the tufts, although no actual count was carried out.

While the glomerular changes just described are present in the large majority of fatal cases of eclampsia (51 of Bell's 53 cases) and most fatal cases of preëclampsia, they are sometimes very slight. In 1 instance of toxemia with death during eclampsia which I examined, the changes in the glomerular loops were, at most, trifling; I do not believe that, from examination of the sections, one would have suspected the condition that had existed during life. Zimmerman and Peters emphasize that while 2 of their 3 necropsies on eclampsia exhibited the changes described above, in the third the glomeruli were not abnormal. It would appear that manifestations of toxemia of pregnancy (proteinuria, edema, hypertension, and even eclampsia) may be present at a time when morphological changes in the glomeruli are not definitely demonstrable by present methods. The pathogenesis of the glomerular lesions is not clear; the possibilities have been suggested that they result from intermittent spasm of the afferent arterioles (Sheehan[23]) or from circulation of a toxic substance, but there is no supporting evidence.

It will be seen in the following that a significant proportion of patients with toxemia of pregnancy continue with hypertension and ultimately develop the classical picture of essential hypertension. In such cases my observations are entirely confirmatory of those of Herrick and Tillman,[6] revealing an arteriolosclerotic kidney not differentiable from that found in essential hypertension in the male (Chapter 24). In some of the cases, there are the arteriolar necrosis and other changes described above as characteristic of the malignant phase of essential hypertension.

Cortical Necrosis.—An extremely rare complication of pregnancy, which may or may not be associated with other evidences of toxemia, is bilateral and almost complete necrosis of the renal cortex. The necrosis is ischemic in origin, and in many of the cases thrombosis of the branches of the renal arteries is present But most recent investigators (*cf* Ash[25]) believe that the basis of the ischemic necrosis is always spasm of the renal arteries, and that the thrombosis is secondary.

Dieckmann[3] found that of 78 reported cases of bilateral cortical necrosis, 72 per cent occurred in pregnant women and 46 per cent had *abruptio placentae*. In these cases it would appear that the immediate cause of the cortical necrosis is spasm of the renal arteries brought about by the hemorrhage. Dieckmann believes that an increased incidence of these cases in recent years is due to longer survival following obstetrical hemorrhage as a result of improved treatment following transfusion. In his experience, cortical necrosis in pregnancy occurs more often in women with preexistent hypertensive and renal disease than in those with toxemia of pregnancy. This was true in the few cases that I have seen.

monal derangement. That this disturbance concerns the placental hormones seems very *plausible*, but remains to be proved. Evidence was cited above (page 948) that regressive changes in the placenta, presumably ischemic in origin, tend to be more marked in toxemia. Much recent speculation (for it is little more) has incriminated placental ischemia in the pathogenesis of toxemia. If hormones secreted by the placenta are concerned in the pathogenesis of toxemia, they are either steroidal in nature or stimulate the secretion of steroids, for there is much in the clinical picture of toxemia of pregnancy, notably the sodium retention and hypertension, which simulates clinical hyperactivity of the adrenal cortex (Cushing's syndrome) and the consequences of injection of desoxycorticosterone-like hormones. Tobian[84] found some indications that increased urinary excretion of "corticosteroids" (determined by a method not necessarily specific) is correlated with edema in pregnancy, but not necessarily with severity of preëclampsia. Attempts have been made to interpret toxemia of pregnancy as a disease of adaptation resulting from stress (page 711), but without other than a speculative basis (*cf.* Selye[83]).

For authoritative surveys of the present status of the hormonal theory of the pathogenesis of toxemia of pregnancy, the reader is referred to the publications of Smith and Smith,[85] Dieckmann[3] and Somerville.[86]

The Relationship of Toxemia of Pregnancy to Essential Hypertension.—Certain clinical data suggest the possibility of an interrelationship between toxemia of pregnancy and essential hypertension:

1 The family history of women with toxemia of pregnancy shows a much higher incidence of essential hypertension than does that of controls.

2 Women of the same bodily habitus are predisposed to both essential hypertension and toxemia of pregnancy. This was clearly brought out in observations[84] made on 120 women with toxemia of pregnancy and 100 normal pregnant controls. A much higher proportion of the women with toxemia of pregnancy than of the normal controls were of thick-set (sthenic) bodily habitus. Moreover, obesity was much more common in the women with toxemia. Quantitatively, these observations were expressed by the finding that the average pregestational weight of the woman with toxemia was 148 pounds while that of the controls was 126 pounds and the average *weight height ratio of the* women with toxemia was 2 5 pounds per inch in contrast to 2 08 pounds per inch in the controls. We have seen (Chapter 25) that the sthenic bodily habitus with marked predisposition to obesity is precisely the constitutional milieu in which essential hypertension most often develops.

3 Several investigations, most notably the studies of Herrick, Corwin and Tillman,[8] have revealed that a remarkably high proportion of women who pass through toxemia of pregnancy ultimately develop essential hypertension. Thus, Herrick and Tillman's follow-up studies of patients with hypertensive toxemia of pregnancy disclosed that 50 per cent have a systolic pressure over 150 mm by the third year after delivery. My own experiences are entirely confirmatory of those of Herrick, Corwin and Tillman,[4] eventually, a majority of women

toxemia of pregnancy is hypertension, and this does not result from, and may even be countered by, hepatic damage.

The Role of Hormonal Disturbances.—The very fact that toxemia of pregnancy occurs most often in women of sthenic constitutional habitus with marked tendency to obesity indicates that aberrations of hormonal regulation may be concerned in the pathogenesis, at least in creating a predisposition. Further evidence along these lines was obtained in an investigation by Vorzimer[34] *et al.* We found that a considerable proportion of women with toxemia of pregnancy present a clinical picture which has many similarities with the Cushing syndrome in the nonpregnant state. The women in question have obesity of girdle distribution with a pudgy face, a stocky build and more or less hypertrichosis of virile distribution. Additional indications that endocrine abnormalities may be concerned in the pathogenesis of toxemia of pregnancy were obtained by the roentgen study of the form of the pelvis. Rappaport[31] found that in women with toxemia of pregnancy the incidence of the true gynecoid pelvis is low and there is a predominance of other types, especially the anthropoid; the frequency of reversion to the male and primitive types of pelvis is high in women with toxemia. Such peculiarities in the form of the pelvis are doubtless of endocrine origin. Another point that may be relevant in this connection is that women with toxemia of pregnancy not uncommonly exhibit an exaggeration of the "acromegaloid" coarsening of the features and enlargement of the nose, hands and feet that may also occur to some extent in normal pregnancy.

In the effort to establish a hormonal pathogenesis of toxemia of pregnancy, the endocrine organs have been extensively investigated. Assays have been carried out in the blood and the urine in both normal pregnancy and toxemia of the levels of pituitary, adrenal, gonadal and placental hormones. Efforts have been made to correlate these hormone levels with the clinical picture and with the state of the placenta, especially the syncytium. A tremendous amount of work along these lines has been carried out over a period of many years by Smith and Smith. Their studies indicate that hormonal dysfunction of the placenta occupies a central position in the pathogenesis of toxemia of pregnancy. Smith and Smith[35] summarize their conclusions as follows: "The evidence at hand appears to establish premature senility of the placental syncytium and premature withdrawal of the placental steroid hormones as the final intermediary pathology. This disturbance, which occurs normally at term, must be brought about prematurely by the working of the primary etiology, which probably involves either an intrinsic metabolic abnormality affecting the placenta or a decrease in blood supply to the placenta or both " Regarding the cause of the suggested placental dysfunction, attempts have been made since the early studies of Young[33] to attribute toxemia of pregnancy to premature and abnormally extensive infarction and other regressive predominantly ischemic changes in the placenta (page 948) To the writer, whose experience with toxemia of pregnancy has been purely as an internist, but who has studied considerable of the obstetrical literature, it seems highly probable that the immediate pathogenetic mechanism of the edema, hypertension and other manifestations of toxemia of pregnancy is a hor-

In the light of these facts, there can be no doub… …mpsia is merely one, albeit the most … …ia of pregnancy. … …have … …ample of … cephalopathy. … …that may occur … …gnant phase of essential hypertension. … conditions—glomerulonephritis, the malignant phase of essential hypertension and toxemia of pregnancy—*when the diastolic pressure* reaches a very high level, it may produce edema of the brain and through the latter headache, cerebral vomiting, amaurosis of cortical origin, convulsions, coma and the other *manifestations* which were gathered together in Chapter 11 under the name of hypertensive encephalopathy. In eclampsia gravidarum, increased intracranial pressure due to edema of *the brain is revealed* by high spinal fluid pressure and often by papilledema; Zangemeister[31] demonstrated the edematous swelling of the brain during life by trephination. That edema of the brain is found at the post-mortem examination of patients who succumb to eclampsia has long been known.

…

nephritis and toxemia of pregnancy—are those in which hypertensive encephalopathy was most apt to occur before the days of salt restriction and has almost vanished since. For a discussion of the possible mechanisms *through which hypertension results in edema of the brain, the reader is* referred to page 354.

At the necropsy of patients who succumb to eclamptic coma, it is not rare to find intracerebral hemorrhage. Dieckmann[1] states that a compilation of available reports indicates that extensive hemorrhage was found in 15 to 20 per cent of all necropsies. However, this figure refers only to fatal cases and perhaps includes patients with pregestational hypertension; intracerebral hemorrhage extensive enough to produce coma has an extremely high mortality (page 806) and the minority who survive usually have residual paralyses, while the vast majority of patients with eclampsia survive and rarely have *residua in the nervous system*. Schmorl,[25] who studied the pathological anatomy of eclampsia for many years, observed petechial hemorrhages in the brains of 58 of 65 fatal cases of eclampsia, but extensive hemorrhage in only 1. Massive *intracranial hemorrhage is* less rare when hypertension is due to pregestational disease than to the toxemia of pregnancy.

THE CLINICAL PICTURE OF TOXEMIA OF PREGNANCY

Toxemia of pregnancy becomes manifest in the last four, almost always the last three, months of *pregnancy*. *Only on* extremely rare occasions, especially in conjunction with hydatidiform mole, do the symptoms appear

clinical or anatomical criteria of which I am aware from essential hypertension in the male. A typical sequence of events is the following: A woman is found early in pregnancy to have normal blood pressure and urine. In the last trimester hypertension develops; this is usually either preceded or followed by proteinuria and perhaps by abnormal edema. Following natural or induced termination of pregnancy, the blood pressure falls, usually but not always to normal. But after a period which varies from a few weeks to several years, the arterial pressure rises and ultimately reaches high levels. In the first years this hypertension is not accompanied by impairment of renal function and there may not even be proteinuria. The subsequent course is also the same as that of essential hypertension unrelated to pregnancy. The hypertension may be asymptomatic for many years but sooner or later trouble appears; the larger moiety of the patients develops either heart failure or angina pectoris, another group suffers apoplexy or other manifestations of cerebral vascular disease, and a small fraction of the patients enters the malignant phase of the disease with necrosis of the renal arterioles and usually death from uremia. Necropsy of patients with hypertension initiated years previously during toxemia of pregnancy reveals the banal findings of essential hypertension, *viz.*, the arteriosclerotic kidney described in Chapter 24.

The nature of the connection between toxemia of pregnancy and essential hypertension disclosed by these clinical observations is entirely obscure. Especially because of the frequency with which toxemia of pregnancy leads to what in a male would be called essential hypertension, the writer for a time believed the toxemia of pregnancy and essential hypertension to be different aspects of the same disease, toxemia representing an acute onset of the disease under the special conditions of pregnancy. However, the preponderant role of water retention in most cases of toxemia renders this view untenable. Essential hypertension is a disease which arises on the basis of a hereditary predisposition, and a plausible hypothesis—but no more—would seem to be that the development of toxemia of pregnancy in a woman with the hereditary basis of essential hypertension evokes the previously latent hypertension

Eclampsia.—For a long time, many differentiated eclampsia as an entity distinct from other forms of toxemia One of the reasons for this differentiation was the belief that if the patient survives, recovery from eclampsia is almost always complete and the disorder does not recur in succeeding pregnancies. This is now known to be incorrect, women who suffer from eclampsia frequently have a very high incidence of preeclampsia in later pregnancies and often develop permanent hypertension Closer clinical observation has shown that in the vast majority of cases, eclampsia is the culmination of a protracted period of toxemia of pregnancy, although it is true that on rare occasions eclampsia breaks out after a relatively short period of hypertension. Moreover, since the introduction of salt restriction into the treatment of toxemia of pregnancy and the interruption of the latter when it becomes worse under observation, there has been an enormous diminution in the frequency of eclampsia, indeed, the terrifying convulsive episodes have almost vanished in hospitals which maintain adequate prenatal clinics, and such cases as are seen are almost always patients who had no prenatal care.

... nd in 6 of these However, this can be no more

may develop ...

Eastman[9]). A possibility that seems *a priori* probable is that the edema of toxemia of pregnancy is due to increased sodium reabsorption by the renal ... result of greater stimulation by salt-retaining steroid hormones. ... ation of

placenta. But that the edema of toxemia represents ... this mechanism, while plausible, remains to be proved. Orloff[42] *et al.* obtained diuresis of salt and water in 1 patient with toxemia of pregnancy by the administration of salt-poor albumin and came to the conclusion that edema in toxemia of pregnancy may be related to both increased tubular reabsorption and diminished colloid osmotic pressure of the plasma. Still to be reconciled with the otherwise plausible view that increased tubular reabsorption of sodium is concerned in the pathogenesis of edema in toxemia is the finding by Freis and Kenny,[43] Dieckmann[3] and others that plasma volume is characteristically low, however, the validity of plasma volume determinations by the methods used under these circumstances is

gations were not confirmed by Byrom and Wilson,[44] Page,[45] Levitt[46] and others While there are observations of increased antidiuretic activity of the urine in toxemia (Teel and Reid[47], Krieger and Kilvington[48]), their significance seems doubtful.

Urinary Changes.—Proteinuria is one of the manifestations of toxemia ...

proteinuria ...

patients, proteinuria preceded hypertension in 4 while in 31 hypertension antedated proteinuria, in 14 they appeared coincidentally. The proteinuria varies from slight to massive According to Eastman and others, the proportion of globulin in the urinary protein is usually higher in toxemia than in glomerulonephritis. Marked proteinuria almost always proves to be indicative of severe toxemia, and increase in proteinuria is to be viewed with concern Proteinuria usually disappears within a matter of days after delivery, but this is not always true and it may persist for months or permanently. The pathogenesis of the proteinuria and its relation to the renal lesions are not known Largely because proteinuria is often preceded

... more than in glomerulonephritis. There are difficulties, however, in reconciling with the angiospastic theory of toxemic proteinuria the finding that renal blood flow is characteristically normal (page 959).

before this time, and may also appear in the first day or two after delivery. The cardinal clinical manifestations are edema, proteinuria and hypertension; the most feared culmination eclampsia; and the most common sequel chronic hypertension clinically and anatomically indistinguishable from essential hypertension. Nowadays, since periodic examination from an early stage of gestation has become the rule, toxemia of pregnancy is very often discovered by the physician before the patient is aware of anything abnormal.

Fluid Retention and Edema.—Fluid retention exceeding the normal for the time of pregnancy and edema are cardinal characteristics of toxemia of pregnancy. The disorder is often first detected because edema is noted or the patient has gained too much weight. The interpretation of fluid retention is, however, rendered more difficult by the fact that considerable degrees may occur in normal pregnancy. Apart from the tendency to swelling of the lower extremities due to mechanical pressure of the uterus, Dexter and Weiss[22] found that 64 per cent of 100 otherwi... gnant ... h and ... rated ... Patients who gain in excess of 600 grams per week are to be watched carefully for other evidences of toxemia and have the sodium content of the diet restricted. Fortunately, abnormally great fluid retention is by no means always followed by other evidences of toxemia. Thus, Dexter and Weiss found that of 75 women pregnant between thirty-two and thirty-six weeks with generalized edema but no proteinuria or hypertension, only 8 subsequently developed these manifestations. On the other hand, it is rare for hypertension or proteinuria to make their appearance without antecedent abnormal fluid retention Of Dexter and Weiss's 31 pregnant women with hypertension or proteinuria, in 24 generalized edema developed previously and in 3 concomitantly; the remaining 4 had gained in excess of 600 grams weekly during the preceding few weeks. In the rare cases in which toxemia develops without antecedent abnormal gain in weight, it may be that fluid retention is counterbalanced by emaciation. The edema of toxemia of pregnancy may reach extreme degrees, but this is rare since sodium restriction has been applied.

The edema of the lower extremities which is so common in normal pregnancy and generally accentuated in toxemia is due to increased hydrostatic pressure in t... pressure in the fem... Contrariwise, the ... not been elicited. ... pressure in the veins of the upper extremities is normal and Dexter and Weiss found the capillary pressure also within normal limits. Nor is the ...

... tion of the edema; the plasma albumin level was between 2.25 and 3.95 per cent in 17 toxemic patients studied by Vorzimer[34] *et al.*, and the albumin/-

disappears as the urinary volume rises with recovery. Bilateral cortical necrosis of the kidneys, of course, quickly leads to renal insufficiency and uremia.

The chief circumstance in which renal insufficiency and great azotemia occur in toxemia is as a result of shock due to hemorrhage, obstetric trauma or other cause. The mechanism presumably involves decrease in renal blood flow due to vasoconstriction in the kidney with resultant tubular necrosis. Maury and Donnelly observed severe oliguria or anuria in 5 per cent of their toxemic cases.[56]

The individual renal functions in toxemia have been studied in considerable detail. Renal blood flow has been found to be characteristically normal in toxemia (Chesley[55] *et al.*, Wellen[56] *et al.*). The glomerular filtration rate is somewhat reduced when compared to post-partum values (Wellen *et al.*). The filtration fraction is normal or low (Corcoran and Page,[57] Wellen *et al.*). Corcoran and Page attributed the lowering of the filtration fraction to the thickening of the walls of the glomerular loops. That tubular function is substantially intact is indicated by the good concentrating ability and the finding of Wellen *et al.* that diodrast T_m is normal.

The uric acid level of the blood is often increased in toxemia. Stander and Cadden[58] found that the increase is roughly proportional to the severity of the toxemia, but this has not been evident in my observations. Chesley[59]

that the decreased uric acid clearance in toxemia is due to increased tubular reabsorption.

Pulmonary Edema.—Acute left ventricular failure with resultant pulmonary edema is a danger in toxemia of pregnancy. According to Moore and Lawrance,[60] almost one-third of the mortality in eclampsia is due to pulmonary edema, but it also ocurs in preeclampsia. Left ventricular failure is most apt to occur in women who had hypertensive disease before preg-

The complica-

ion, and may

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circulation are raised. The clinical manifestations of acute left ventricular failure in toxemia of pregnancy are similar to those of other forms of hypertensive disease (page 777).

Retinal Changes.—These develop in toxemia

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) and appear only in

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The first opthalmo-

Casts of various descriptions usually accompany the proteinuria. In most instances of toxemia the sediment contains few cells (by the usual method of examination), but sometimes they are present in moderate numbers. Elden[51] *et al.* found the Addis count of casts, red cells, white cells and epithelial cells increased in the acute stages of toxemia. Uncomplicated toxemia of pregnancy rarely, if ever, causes gross hematuria such as may occur in glomerulonephritis.

The water retention is manifested by oliguria. When the edema clears up, the urinary volume rapidly rises so that there may be marked polyuria for a few days; the latter is one of the most reliable indices of improvement. Oliguria often heralds eclampsia. Cortical necrosis is marked by anuria.

Hypertension.—Rise in blood pressure is the most redoubtable of the three cardinal manifestations of toxemia—hypertension, edema and proteinuria. There are many patients with toxemia, as proved by proteinuria and abnormally great fluid retention, in whom the blood pressure never rises above normal limits. However, even in these, careful observation usually shows that the blood pressure is a little higher than it was before pregnancy. It is to be remembered that in normal pregnancy the blood pressure is normal or falls a little during the middle months, to return to the prepregnant level or perhaps a little higher in the last months; with the labor pains, of course, the blood pressure rises

Rise in blood pressure is very often the first indication of toxemia; for this reason measurement of the arterial tension should not be neglected at each prenatal examination. A sudden rise in blood pressure may precede eclampsia. Above were mentioned the many cases in which hypertension antedates proteinuria, and patients are not rare in whom toxemia of pregnancy is manifested by hypertension developing in the last weeks of pregnancy without proteinuria appearing at any time; usually, however, unless averted by salt restriction, there is abnormally great fluid retention. The hypertension of toxemia varies from slight to great. It is often intermittent, especially in the early stages, disappearing on bed rest and sedation. Only very rarely does the hypertension enter the malignant phase during pregnancy, although this may occur in subsequent years in persistent hypertension initiated during toxemia. Both the systolic and diastolic pressures are elevated, but at the start the rise is most often definite in the systolic value. Attempts have been made to use the reaction of the blood pressure in the cold pressor test (page 764) to foretell toxemia in suspected subjects (*cf.* Browne[52]) However, observations by Chesley and Chesley[53] and Reid and Teel[54] show that the response is inconstant and the incidence of toxemia not correlated with hyperreaction.

Renal Function.—Th
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test and nonprotein nitrogen of the blood within or close to normal limits in all. The same is true of the urea clearance. With extreme oliguria in
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...en discussed in Chapter II. The cerebral ... peated, are consequences of hypertension, although the formation of ...lema of the brain is doubtless favored by the general tendency to water ...tention which is present. I have never seen an instance of eclampsia ... blood pressure was not elevated, and would regard reported ...

... of the liver, as is often stated, does not seem to have been ... Sudden gain in weight of over two pounds a week always calls for careful

... the usual tests of hepatic ... , although the disturbance is rarely severe. This is an exaggeration of a tendency which is not rarely found toward the end of normal pregnancy. Thus, Phillpot[69] *et al.* found that the cephalin cholesterol flocculation test gave what they regarded as abnormal results in 6.5 per cent of normal pregnant women and 33 per cent of those with toxemia. Dieckmann[70] and his associates observed that in the last trimester of pregnancy cephalin flocculation was abnormal in 19 ...

... of uncomplicated pregnancies and 31 per cent of preëclamptics. Bromsulfalein retention occurs in some but not all patients with severe toxemia.

... degree seems to be extremely small. Dieckmann states that jaundice occurs in less than 1 per cent of eclamptic patients and that among them the mortality is 31 per cent. That the hepatic lesions of the edematous and hypertensive toxemia of pregnancy ever goes on to acute yellow atrophy does not seem to have been demonstrated. On extremely rare occasions, the hepatic lesions of toxemia of pregnancy have led to rupture of the organ with hemoperitoneum (*cf.* Weintraub,[71] Burton-Brown and Shepherd[72]).

PROGNOSIS OF TOXEMIA OF PREGNANCY

Nowadays, it is rare for the mother to succumb to toxemia during pregnancy. The reason is that prenatal observation usually results in early detection of the disorder with appropriate treatment; and under these circumstances eclampsia, *the great danger of the* woman with toxemia, is a rarity. Furthermore, transfusion has enormously improved the *outlook* in hemorrhage from *abruptio placentae*. Zangemeister's older figures gave the incidence of eclampsia as 18 per cent in primiparae and 4 per cent in multiparae with toxemia of pregnancy. At present, the incidence of ec-

scopic change is narrowing of the retinal arteries. This is demonstrable in a high proportion of cases of toxemia of pregnancy with hypertension by comparison with the findings after the hypertension has subsided (*cf.* Gibson,[62] Gordon[63]). Hallum[64] found hypertensive retinopathy in 4 per cent of cases with blood pressure below 150/100 mm., 10 per cent of those between 150/100 and 175/125, and 33 per cent of those over 175/125 mm. The ophthalmoscopic appearances are the same as those in all types of hypertensive retinopathy (page 368). Spasms of the retinal arteries are common and have been photographed before the retinal lesions have developed (Haselhorst and Mylius[65]). Indeed, the latter need not necessarily follow. Mylius[66] showed
and retinal
changes in t due to toxemia of pregnancy is more apt than other forms of this retinal lesion to be complicated by detachment of the retina; this is probably due to the general fluid retention favoring accumulation of fluid behind the retina. Usually the retina re-attaches within days or weeks, but sometimes this does not occur and vision is permanently impaired. The proportion of toxemic patients with retinopathy who develop chronic hypertensive disease is high (11 of Wagener and Keith's[67] 14 cases).

Recently,
lonephritis, ap-
pearance; it seems to be covered by a thick film of fluid." I have not yet had opportunity to study this sign and its differentiation from the prominent light reflexes usual in the young."

Eclampsia.—The most dreaded manifestation of toxemia of pregnancy is eclampsia. Fortunately, with present-day treatment, eclampsia has become a great rarity in patients under prenatal care. In 7500 deliveries in Beth Israel Hospital in the past three years, there has been only 1 instance of eclamptic convulsions. Eclampsia almost always occurs in a woman who has had a considerable period of well-marked symptoms of toxemia of pregnancy. However, there are rare cases in which up to the very onset of the convulsions the urine was devoid of protein and there was no edema. It is to be presumed, however, that in such cases measurement of the blood pressure shortly before the onset of the seizure would have revealed hypertension. While it is theoretically conceivable that edema of the brain as a part of generalized anasarca could produce eclampsia, I have not seen such a case; every eclamptic patient I have observed had hypertension

In accord with the incidence of toxemia, eclampsia occurs in the later months of pregnancy, during labor, or soon post-partum. It is generally stated to occur most frequently during labor, but Williams[16] and Stander[68] think this is because the convulsions tend to induce labor. To the writer it would seem, since eclampsia is due to hypertension, that the additional marked rise in blood pressure during the pains may well precipitate the cerebral symptoms. Stander states that about one-half of the cases occur during pregnancy, and one-quarter each during labor and post-partum. He believes that the latest period at which true eclampsia occurs is about four days after delivery.

whose toxemia was marked by systolic blood pressure not exceeding 160 mm. and slight or absent proteinuria, about one-third developed permanent hypertension. In a follow-up period averaging 5.6 years after the toxemia, Herrick and Tillman found that the mortality was more than 6 times the expected; 80 per cent of the deaths were within the cardiovascular-renal field. My own [illegible] *with those of Herrick and his associates.* [illegible]

pregnancy, the greater [illegible] pressure For this reason, there seems good reason to believe that the incidence of post-toxemic hypertension is lessened by intervention at an early stage of hypertensive toxemia. Thus, Chesley[73] *et al.* find that in recent years their incidence of post-eclamptic hypertension has been reduced by half, which they suggest may be due to more radical management of preeclampsia But even with relatively early intervention, the main toll of toxemia is exacted long after pregnancy is terminated. One unknown in the high incidence of hypertensive disease *following toxemia* is the proportion of patients who have the inherited predisposition to essential hypertension (page 695), even though it was not evident at the start of pregnancy

It has been widely held that eclampsia in one pregnancy is *rarely followed by correlated trouble in succeeding gestations* This is not correct. In 154 multiparas with toxemia studied by Corwin and Herrick, 13 per cent had a history of convulsions in previous pregnancies. Chesley *et al.* found that 45 per cent of women with eclampsia had at least one subsequent toxemia.

Fetal mortality is increased in toxemia of pregnancy In comparison to a fetal mortality for his general clinic population of 5.5 per cent, Peckham[74] observed a fetal mortality for the mildest forms of toxemia of 9.46 per cent, which increased with greater severity of toxemia until it was 48 per cent in eclampsia Especially important are Peckham's figures showing that the earlier in pregnancy toxemia develops, the higher the fetal mortality. McLane[75] states that after thirty-two weeks the longer the fetus remains *in utero*, the greater the fetal mortality, this has also been my experience.

TREATMENT OF TOXEMIA OF PREGNANCY

Frequent prenatal examination is the key to early *recognition* of toxemia, which is prerequisite to optimal treatment It goes without saying that detection of hypertension, proteinuria, unusual edema, excessive gain in weight, or other evidence of definite or probable toxemia calls for especially close observation In fact, as soon as the diagnosis of toxemia is made, the wisest procedure is often to put the patient to bed, at least until the course can be determined.

Toxemia is Not to be Treated as a Form of Renal Insufficiency.—The treatment of toxemia of pregnancy was long dominated by the conception that impairment of renal function plays a significant part in the disease Hence the patient was treated as though she were in danger of developing renal insufficiency and uremia. In the effort to avert this, large volumes of

lampsia is so small that a year may pass on a large maternity service without an in-patient developing eclamptic convulsions. This is the more striking because there is no reason to believe that the incidence of toxemia itself has lessened, although salt restriction renders it much more often asymptomatic; in fact, the incidence may be greater because limitation of families results in a higher proportion of primiparae. The seriousness of eclampsia is indicated by Stander's figures,[68] prior to 1929, which revealed a maternal mortality of between 10 and 20 per cent; at present, the mortality in hospitals is much less than half of this—an improvement due to therapeutic advances. Probably the most frequent cause of death in eclampsia is acute left ventricular failure with resultant pulmonary edema. This occurred in 26 of the 46 fatal cases of eclampsia collected by Teel and Reid. Hemorrhage and infection formerly took a large toll, which has been enormously lessened. The fetal mortality in eclampsia has been reported to range between 20 and 60 per cent, with an average of 35 per cent, and quite

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rise in blood pressure *above the level obtaining early in pregnancy*, and especially one which does not yield quickly to bed rest and sodium restriction, is always to be viewed with concern. When it occurs before the period of viability, the chances are against successful termination of pregnancy with a living baby. A given level of hypertension seems to be the more serious, the more it is above the pregestational level, if the patient had essential hypertension before pregnancy and the blood pressure does not rise, the chances of completing pregnancy with a viable baby are better. Steadily increasing hypertension is a warning of the possibility of eclampsia, although nowadays the latter can almost always be averted The prodromes of eclampsia include headache, irritability, nausea, vomiting, blurring of vision, photophobia, epigastric pain and oliguria.

Hypertensive retinopathy bespeaks very severe toxemia, and calls for interruption of pregnancy. Hallum found that if retinopathy occurs before the twenty-eighth week, there is only about a 25 per cent chance of obtaining a live baby even if the pregnancy is continued to the period of viability and "there is almost 100 per cent chance of permanent vascular-renal damage developing"

Termination of pregnancy is usually followed by quick improvement of the mother even though the symptoms of the toxemia were very severe and the outlook may have seemed desperate during eclampsia. But despite this rapid improvement, the chances unfortunately are very considerable that the patient will gradually develop hypertensive disease indistinguishable clinically or morphologically from essential hypertension in the male. Our knowledge of this very important fact is largely due to the careful observations of Herrick, Corwin and Tillman,[6] carried out over a long period of years. These reveal that about one-half of women who have toxemia of pregnancy develop hypertensive disease within three years. Especially important is their finding that the incidence of hypertensive disease is considerable after even "mild" toxemia. Among their patients

order to combat hypo-albuminemia and favor diuresis. The technique of the low sodium diet is discussed on page 175.

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by ... ...—Often ... observation ... ...mai- mat ... owed tion ... ipto- visa ... ...nstra- ... other sedatives is usually ad-

Hypotensive Drugs.—The consequences of hypertension are the great dangers in toxemia of pregnancy. For this reason, every effort should be made to combat high blood pressure. If not pronounced, sodium restriction, rest and hypotensive drugs should be used. Veratrum preparations (Meilman,[90] and Alban[91] *et al.*) and hydralazine (Assali and Suyemoto[92]) have been found of great value. In ... eously low... ... it hexamethonium subcutan- ... ure and apparently averted ... hese drugs, which *should be* ... Chapter 29

...ment.—In view of the great probability that toxemia of pregnancy is primarily a hormonal derangement, it is disappointing that treatment with hormones has not proved of value. Smith and Smith obtained some evidence that administration of diethylstilbestrol to large numbers of pregnant women from the twelfth to the thirty-sixth weeks lessens the incidence of toxemia. Early reports of favorable therapeutic effects from estrogen and progesterone in the treatment of toxemia have not been borne out (Smith and Smith,[25] Taylor[42])

Interruption of Pregnancy.—This is generally the most important, and often the most difficult, question to be decided in the management of a woman with toxemia of pregnancy. Puzzling as are the medical problems involved, they are often outweighed by religious, sociologic and emotional considerations. In reaching a decision, two desiderata, one regarding the baby and the other the mother, seem especially important:

1. Fetal mortality is high in toxemia of pregnancy (page 962). Moreover, the above-mentioned studies of Peckham showed that fetal mortality increases in proportion to the severity of the toxemia and that the highest fetal mortality occurs in the cases allowed to progress the longest time between the appearance of toxemia and delivery.

2. As regards the mother, one must always bear in mind the fact mentioned above (page 962), which was not sufficiently appreciated by previous generations, that the proportion of women with toxemia who subsequently develop hypertensive disease and die prematurely as a result of it is exceedingly high. Moreover, it is very probable, although I know of no

sugar and salt solution were administered and protein rigidly *restricted in the diet.* A regimen better calculated to aggravate the manifestations of toxemia could hardly be devised, and I feel confident that in many patients with toxemia, eclampsia and heart failure *were precipitated by saline* infusions and favored by a *diet in which protein* was restricted and salt was not.

It was seen above that in patients who enter pregnancy without impairment of *renal function*, the latter does not suffer significantly during toxemia. There is therefore no need to institute measures to combat renal *insufficiency*. It was further pointed out that fluid retention is not only responsible for the peripheral edema but is also concerned in the pathogenesis of cerebral edema and heart failure—the *great dangers in toxemia, in* addition to *abruptio placentae*. The most important measure in combating fluid retention is sodium restriction in the diet, and the saline infusions formerly in vogue are strongly contraindicated. Moreover, *since renal* function is adequate, the protein restriction formerly routine is not called *for* Indeed, protein restriction is probably harmful, for the hypo-albu*minemia* present in almost all the cases plays an accessory role in favoring water retention, and this is abetted by *protein restriction. A low protein* intake is contraindicated with especial emphasis when much protein is *being* lost as a result of proteinuria—and it is just under these circumstances that protein was eliminated from the diet in the past.

Combating Fluid Retention.—Some degree of fluid retention is *physiological* in the last trimester of pregnancy and is most often *greatly augmented in toxemia*. Fluid retention plays a great part in the causation of the manifestations of toxemia Strauss[76] showed that the fluid retention is augmented by increasing and lessened by lowering the sodium content of the diet. He found that when water is eliminated as a result of diminished sodium intake, the symptoms of toxemia, including the hypertension, are alleviated. Contrariwise, when Strauss gave large quantities of sodium *chloride to 10* pregnant women with hypertension and hypoproteinemia, they gained in weight, palpable edema appeared and the arterial pressure rose, in 5 proteinuria increased and in 3 symptoms of preeclampsia appeared. Dieckmann also showed that in the preeclamptic patient the injection of 20 to 25 grams of sodium chloride in solution daily for two or more days will cause an increase in proteinuria, blood pressure and edema. These observations show with great clarity the enormous importance of sodium restriction in the management of toxemia of pregnancy.

To the writer it appears that sodium restriction is the most notable advance yet achieved in the treatment of toxemia of pregnancy. When rigidly enforced from an early stage of the disease, it reduces the incidence of heart failure and eclampsia to extremely low levels; I have not seen eclampsia develop in a patient who had been on adequate sodium restriction for over a week. Sodium restriction should be accompanied by adequate water intake, usually about 2500 cc. per day (page 172). In fact, Turner[77] *et al.* achieved good results in eclampsia by the intravenous administration of 4000 cc. daily of isotonic glucose solution, a method of treatment akin to Schemm's regimen in congestive heart failure (page 173). The protein intake should also be ample—usually about 100 grams daily or more—in

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amytal. This should be ...
6 cc. of a 50 per cent solution of magnesium sulfate (page ...). ... convulsions have been controlled, sedation may *be maintained by rectal* administration of 2 to 3 grams of chloral hydrate or 30 cc. of paraldehyde, or 4 cc. of the latter may be given intramuscularly. After the convulsions have been controlled, at least for the time being, a hypotensive drug should be administered if the blood pressure is high. Veratrum preparations, *hydralazine or hexamethonium* may be used; details regarding their administration will be found in Chapter 29. None of the six eclamptic ... with injections of protoveratrine had ... ickly become cyanotic, she ... ch should be kept for acute ... This calls for intravenous digitalization and perhaps phlebotomy; if the patient is not anuric, a mercurial diuretic should be injected. Fluid balance is maintained by intravenous infusion of 10 per cent fructose solution. Since almost all eclampsia patients have high cerebrospinal fluid pressure due to edema of the brain, lumbar puncture has been extensively used for treatment. *However, its value does not seem to be established* and there is danger of herniation of the swollen brain into the foramen magnum (page 362). *Continuous spinal and caudal anesthesia* have been used in the treatment of eclampsia (Whitacre,[80] McElrath,[81] Andros[82]). But the use of the above mentioned hypotensive drugs would seem preferable. What seems to be the optimum tim...
accomplished by
the obstetrician.
toxemia of pregnancy and eclampsia, the reader is referred to Dieckmann's[8] *monograph.*

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detailed statistical proof, that the incidence of subsequent hypertensive disease bears some proportionality to the length of time the hypertension persists during pregnancy.

In the light of these two considerations, I believe that excessive conservatism has often been displayed regarding the termination of pregnancy in women with toxemia. As soon as the diagnosis of toxemia of pregnancy is established, the woman should be put to bed and sodium restriction and the other measures just described put into effect. If under this regimen the definitely elevated blood pressure does not fall within two weeks and the patient does not improve, pregnancy should be terminated. The only exception is at that stage of pregnancy at which it seems that a few weeks may render the fetus viable and when a baby is urgently desired. Here, perhaps, the hope of obtaining a viable baby may justify waiting a short time even though the patient does not improve. But if she is definitely before or after the period of viability and does not improve strikingly on the above measures, pregnancy should be terminated. For before the period of viability there is great doubt that one can wait long enough to obtain a viable baby and meanwhile the mother's vascular system is, in all probability, suffering irreparable damage After the period of viability, if the mother does not improve rapidly on rest and sodium restriction, further procrastination adds little, if anything, to the chances of the baby when one considers the possibility of intra-uterine death and accidental hemorrhage, and subjects the mother to further vascular damage. From the point of view of the mother, the question of premature delivery is largely one of balancing the potential deleterious effects of the procedure against the progressive vascular damage that results from continued toxemia plus the possibility of later having to terminate pregnancy under

obstetrician in accord with the circumstances of the individual case

Treatment of Eclampsia.—Great progress has been made in both the prophylaxis and the treatment of eclampsia. As a result of the institution of prenatal clinics with frequent examination of the weight, blood pressure and urine, toxemia is detected at early stages, and the measures described above instituted In consequence, very few women are allowed to go on to the development of actual eclampsia, and convulsions and coma are a rarity among patients who attend a prenatal clinic.

Such possible precursors of eclampsia as fall in urinary volume, rise in blood pressure, intense headache, epigastric pain, nausea and vomiting, or blurring of vision call for prompt measures. The patient should be kept in a quiet, dark room and amply sedated with a barbiturate and or chloral hydrate. Sodium should be rigidly restricted in the diet. Magnesium sulfate is to be given by injection (page 362). If the blood pressure rises to such levels as 180/110 mm. or more, a hypotensive drug (hexamethonium, hydralazine, alkavervir) is to be given by injection with great caution (*cf.* Chapter 29).

The guiding principle in the treatment of eclampsia is termination of pregnancy at the safest possible time. In the large majority of instances,

. . . ral treatment before initiating the termination

amytal This should be supplemented by the . . . 6 cc. of a 50 per cent solution of magnesium sulfate (page 362). After the convulsions have been controlled, sedation may be maintained by rectal administration of 2 to 3 grams of chloral hydrate or 30 cc. of paraldehyde, or 4 cc. of the latter may be given intramuscularly. After the convulsions have been controlled, at least for the time being, a hypotensive drug should be administered if the blood pressure is high Veratrum preparations, hydralazine or hexamethonium may be used, details regarding their administration will be found in Chapter 29. None of the six eclamptic patients treated by Meilman[80] with injections of protoveratrine had further seizures Since the patient may quickly become cyanotic, she should be kept in an oxygen tent. Close watch should be kept for acute left ventricular failure with pulmonary edema This calls for intravenous digitalization and perhaps phlebotomy, if the patient is not anuric, a mercurial diuretic should be injected Fluid balance is maintained by intravenous infusion of 10 per cent fructose solution. Since almost all eclampsia patients have high cerebrospinal fluid pressure due to edema of the brain, lumbar puncture has been extensively used for treatment However, its value does not seem to be established and there is danger of herniation of the swollen brain into the foramen magnum (page 362). Continuous spinal and caudal anesthesia have been used in the treatment of eclampsia (Whitacre,[80] McElrath,[81] Andros[82]). But the use of the above mentioned hypotensive drugs would seem preferable. What seems to be the optimum tim . . .
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